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Management of Gastroesophageal Reflux Disease

Nasir Khokhar

Gastroesophageal reflux disease (GERD) is a condition in which gastroesophageal reflux (GER) causes either esophageal mucosal injury, annoying symptoms, or both. It is classified into reflux esophagitis (RE) with esophageal mucosal injuries and non-erosive reflux disease (NERD) with symptoms alone.¹

GERD is among the commonest conditions encountered in daily clinical practice. The prevalence varies in different geographic areas; however, it is estimated to be 10% in the general adult population.¹ A Pakistani study reported a prevalence of GERD in rural women to be 64.11%, out of these, 54.6% had GERD with a high impact on life.² It can interfere with physical activity impairing social functioning, disturbing sleep and reducing work productivity.

GERD typically manifests as heartburn and regurgitation, but may also present with atypical symptoms as noncardiac chest pain or extra-esophageal symptoms. Extraesophageal reflux (EER) is a subset of GER that leads to troublesome symptoms/conditions that are not normally attributed to the esophagus.¹ The severity of GERD symptoms does not always correlate with the endoscopic severity of mucosal injury.³ The excessive exposure of the esophagus to gastric acid due to GER is a major cause of esophageal mucosal injury, the extent of which increases with the severity of RE.

Physicians should be aware of potential extraesophageal manifestations of GERD and should inquire about such disorders including laryngitis, chronic cough, asthma, chest pain and dental erosions in GERD patients.⁴ Many patients with these symptoms present to ENT surgeons, pulmonologists cardiologists or dentists.

GERD is generally diagnosed by a combination of clinical symptoms, and responses to anti-secretory therapy. A wide variety of self-administered questionnaires has been developed for the assessment of reflux symptoms to establish the diagnosis and measure responses to treatment.³ A survey of many Asian countries found that the most important factor in diagnosing GERD was the presence of symptoms.³

Upper gastrointestinal endoscopy is not essential in all patients and is generally reserved for those who are refractory to proton pump inhibitor (PPI) or have alarm symptoms like dysphagia, weight loss and EES. Ambulatory esophageal reflux monitoring and other

sophisticated diagnostic tests should be left to the specialists.

Acid suppression with PPIs is the mainstay of pharmacologic therapy for GERD. The “PPI test” may be applied for cases without endoscopy. In cases in which symptomatic resolution is achieved with PPI, treatment may be discontinued. If symptoms persist or relapse, endoscopy may need to be performed.

The PPI test is a practical approach in clinical practice due to its limited invasiveness, lower cost, and symptomatic response corroborating a clinical suspicion of GERD. It is a useful diagnostic test for patients presenting with typical reflux symptoms.⁴

More recently, potassium-competitive acid blocker (P-CAB) like vonoprazan have become available and is remarkably effective. Initial recommended treatment for severe GERD is 20 mg vonoprazan for 4 weeks. In cases of response to vonoprazan, maintenance therapy using 10 or 20 mg vonoprazan, or combination with prokinetics needs to be used to prevent the development of complications.^{4,5} A study from Pakistan reported that the symptomatic relief of GERD after 2 weeks of therapy with Esomeprazole and Dexlansoprazole was the same.⁶ PPI and/or P-CAB were prescribed as the therapeutic agent for initial therapy in >90% of GERD patients in China, Indonesia, Japan, South Korea, and Singapore.³ PPI or P-CAB were also prescribed as the therapeutic agent for maintenance therapy with high frequency in all countries, and a half dose of PPI or PCAB was prescribed in around 50% of the patients who needed maintenance therapy.³

PPI-resistant GERD and P-CAB-resistant GERD may be related to reflux or nonreflux causes. The latter includes functional heartburn, eosinophilic esophagitis, esophageal motility disorders, and psychological comorbidity.⁴ Such patients should be referred to specialists for further appropriate management. Surgical or endoscopic options should be considered very carefully in selected cases with multidisciplinary approach and patients should be fully informed about risks, benefits and alternatives.

While PPIs are very effective treatment for GERD, they have been implicated in many side effects after prolonged use. These include bone fractures, pneumonia and renal damage.⁴ Long-term use of PPIs can lead to increased

gastric pH and hypochlorhydria, which may result in significant vitamin (B₁₂ and C) and mineral (iron, calcium and magnesium) deficiencies,⁷ which needs gastric acid for their absorption and bioavailability. Long-term use by the pregnant patients may impose a potential risk of congenital malformations.⁴ The hypochlorhydria by chronic PPIs use may induce hypergastrinemia, which ultimately may lead to the gastric polyps, gastric carcinoids and gastric cancer.⁷ Therefore, caution should be used when they are prescribed for long time. Smallest effective dose and every other day or as needed approach may be advisable.

Histamine 2 receptor antagonists (H2RA) can be used in mild cases. H2RA were used in about 20% of patients needing maintenance therapy in Hong Kong.³ Alginate or antacids for temporary symptom relief can be administered to patients with mild RE and NERD. Prokinetics are not prescribed as maintenance therapy.

Among the most difficult aspect of GERD management is life style issues. Obesity, smoking, alcohol, inactivity and dietary factors like excessive intake coffee, tea and irregular and spicy meals are among the most difficult to manage in clinical practice.⁸

Lifestyle modification measures including avoidance of refluxogenic foods, food avoidance for at least 2–3 hours before going to bed, positional changes during the sleep period, and weight loss have been proposed for management of GERD. Fatty, fried and spicy foods, chocolate and citrus fruits should be avoided. Eating large and late evening meals have been shown to contribute to reflux.¹ Head of bed elevation as well as left lateral decubitus position have been shown to improve nocturnal esophageal acid exposure.¹ Obesity is significantly associated with reflux symptoms and erosive esophagitis and weight loss was associated with a reduction in symptoms and esophageal acid exposure.¹

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REFERENCES

1. Iwakiri K, Manabe N, Ihara E, Kuribayashi S, Akiyama J, et al. Evidence-based clinical practice guidelines for gastroesophageal reflux disease 2021. *J Gastroenterol* 2022;57:267–285.
2. Sarwar F, Saleem M, Zaidi FZ. Prevalence of Gastroesophageal Reflux Disease in rural women presenting to a primary care hospital. *Rawal Med J* 2021;46:533-7.
3. Hojoa M, Nagaharaa A, Hahmb KB, Iwakiric R, Watanabed T, Rani AA, et al. Management of Gastroesophageal Reflux Disease in Asian Countries: Results of a Questionnaire Survey. *Digestion* 2020;101:66–79.
4. Chen JW, Vela MF, Peterson KA, Carlson DA. AGA Clinical Practice Update on the Diagnosis and Management of Extraesophageal Gastroesophageal Reflux Disease: Expert Review. *Clinical Gastroenterology and Hepatology* 2023;21:1414–1421.
5. Jung HK, Tae CH, Song KH, Kang SJ, Park JK, Gong EJ, et al. 2020 Seoul Consensus on the Diagnosis and Management of Gastroesophageal Reflux Disease. *J Neurogastroenterol Motil* 2021;27: 453-81.
6. Ayub JU, Qaisar A, Amin S, Zaman M, Shah AZ, Ahmed F. Clinical Efficacy of Dexlansoprazole vs Esomeprazole in Gastro-Oesophageal Reflux Disease: a Randomized Clinical Trial. *J Saidu Med Coll* 2022;12:112-7.
7. Koyyada A. Long-term use of proton pump inhibitors as a risk factor for various adverse manifestations. *Therapie* 2021;76:13-21.
8. Yuan S, Larsson SC. Adiposity, diabetes, lifestyle factors and risk of gastroesophageal reflux disease: a Mendelian randomization study. Adiposity, diabetes, lifestyle factors and risk of gastroesophageal reflux disease: a Mendelian randomization study. *Eur J Epidemiol* 2022;37:747-54.

Does serum vitamin D status reflect the severity of asthma? A comparative case control study

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Objective: To determine the role of vitamin D in adult-onset asthma by estimating and comparing it with that of healthy controls and to associate it with lung function test.

Methodology: This case control study was conducted in the Department of Physiology, University of Karachi. Cases were recruited from Jinnah Hospital. A total of 280 individuals were categorized into asthmatics and non-asthmatics. History of respiratory illness, D₃ intake, drugs that alter serum D₃, pregnant and lactating mothers were excluded from study. Asthmatics were included according to GINA guidelines. BMI, Spirometry, and serum 25(OH)₂D estimation were performed. Statistically, results were analyzed by SPSS 21.

Results: Difference of BMI and 25(OH)₂D between

two groups were statistically significant ($p < 0.001$). Within controls, 47 had moderate and 93 had mild insufficiency. In cases, 40 mild asthmatics had moderate insufficiency and in moderate asthmatics, out of 50, 12 were severely and 38 were moderately insufficient of vitamin D. In severe asthmatics, 44 had severe while 6 had deficiency of vitamin D. Study revealed that 25 hydroxy D was directly proportional to FEV₁ and FEV₁/FVC in asthmatics ($p < 0.001$).

Conclusion: Vitamin D has pronounced effects on asthmatic condition by its immunomodulatory functions. Intake of this vitamin may improve the inflammation of airways and thus may affect the prognosis of asthma.

Keywords: Asthmatics, immune-modulatory, inflammation, spirometry, Vitamin D, insufficiency.

INTRODUCTION

Asthma is the inflammation of airways that causes constriction of bronchioles, cough and wheeze.¹ About 334 million persons are affected by asthma worldwide. In Pakistan, due to migration of people from rural to urban areas and lack of health facilities, 20% children suffer from asthma.² Adult asthmatics may have a history of childhood asthma or allergy may be due to different causative agents.

To diagnose asthma, pulmonary function tests (PFTs) are performed. Among different parameters of PFTs, ratio between forced expiratory volume in first second/forced vital capacity (FEV₁/FVC%) shows airflow obstruction. Its normal value should be greater than 80%. Another significant parameter of PFTs is forced expiratory volume in first second (FEV₁). In adult form of asthma, difference in FEV₁ >12% and >200 ml from baseline reading shows significant result in the diagnosis and severity of asthma.³ In pathogenesis, airways are blocked due to increase production of mucus. T helper cells of type 2, cause eosinophilic infiltration in airways, hyper-reactive bronchi and IgE antibody secretion in response to allergen.⁴

25 dihydroxy cholecalciferol is also called sunshine

vitamin. Insufficient levels of Vitamin D are a worldwide health issue affecting people of all ages.⁵ Low level of serum 25(OH)D was seen in different viral, bacterial and tuberculous infections.⁶ The active form of vitamin D is 1,25 dihydroxy D₃ and has strong attraction for vitamin D receptor.⁷ 1,25(OH)₂D is controlled mainly by PTH in kidneys, which regulates 1 α hydroxylase. When serum vitamin D level decreases, this enzyme is increased by kidneys. In contrast to this, extra renal site of vitamin D production for example in immune system, depends on serum 25(OH)D. The production of 1 α hydroxylase is under the control of cytokines particularly interferon gamma.

Vitamin D enhances the production of cathelicidin and defensins and provides natural innate immunity.⁸ Decreased serum vitamin D was related to the acute respiratory tract infections,⁹ and vitamin D (VD) deficiency may alter defense mechanism of respiratory system.¹⁰ Vitamin D causes reduced antigen presentation and inhibition of IL-17.¹¹ IL-17 causes movement of neutrophils and eosinophils to the airways resulting in bronchoconstriction and asthma. Production of antibodies by B lymphocytes is also inhibited by VD. All these effects results in reduced inflammation in the

airway.¹² The goal of this work was to estimate and compare serum VD in asthmatic and non-asthmatic healthy subjects and within sub-groups of cases and to find out its relationship with severity of asthma and lung functions.

METHODOLOGY

This prospective case control study was conducted in the Department of Physiology, University of Karachi from 2016-2020 with the collaboration of Jinnah hospital, Karachi. Simple random selection of asthmatic subjects was done after approval of ethical review board of hospital (NO.F.2-81/2019-GENL/34790/JPMC). Overall, 280 subjected of 20-

Table 1: Characteristics of study participants.

Parameters		Control group n(140) Mean±SEM	Case Group n(140) Mean±SEM	p-value
Age (years)		38.81±0.98	41.10±0.94	0.09
Gender	F	81(57.8%)	60(42.8%)	
	M	59(42.1%)	80(57.1%)	
BMI (kg/m ²)		20.69±0.35	24.78±0.39	0.0001
25 Hydroxy D (ng/ml)		23.11±0.14	16.32±0.26	0.0001

Table 2: Comparison of vitamin D in control group and sub-groups of asthma.

Parameters	Control Group n (140)		Mild asthma n (40)		Moderate asthma n (50)		Severe asthma n (50)	
	n	Mean±SEM	n	Mean±SEM	n	Mean±SEM	n	Mean±SEM
Deficiency (<10ng/ml)	Nil	--	Nil	--	Nil	--	6	7.97±0.98
Severe insufficiency (10-16ng/ml)	Nil	--	Nil	--	12	15.54±0.18	44	13.90±1.43
Moderate insufficiency (17-22ng/ml)	47	21.11±0.50	40	19.76±1.05	38	17.01±0.61	Nil	--
Mild insufficiency (23-29ng/ml)	93	24.11±1.17	Nil	--	Nil	--	Nil	--

60 years age both genders were enrolled and equally categorized into asthmatic group and non-asthmatic control group. Asthmatics were sub-divided into mild, moderate, and severe cases. Subjects with previous chronic respiratory illnesses, history of D₃ intake, drugs that may alter serum D₃, pregnant and lactating mothers were excluded from the study.

Asthmatics were included as case group according to guidelines of GINA (GINA, 2019).¹³ BMI was calculated of all subjects by stadiometer by applying the formula of weight (Kg)/height(m²).

25(OH)₂ D was estimated by 25 hydroxyl total ELISA kit. Lung functions were performed by computerized vital graph spirometer (model 6600, Ennis company, Ireland). Flow head was attached to the spirometer. All the essential data was completed according to the guidelines

Table 3: Relationship of 25 hydroxy D with Lung Function Test.

Parameters	Control group n (140)		Case group n (140)	
	(r value)	p value	(r value)	p value
FEV1(L)	0.102	0.29	0.298	0.0001
FVC(L)	0.057	0.49	0.047	0.56
FEV1/FVC (%)	0.079	0.35	0.635	0.0001

of spirometer after appearance of new subject icon on screen. Forceful expiration was performed. Best values of FVC, FEV1 and FEV1/ FVC were taken.

Statistical Analysis: The data analysis was performed by SPSS version 21. To compare continuous variables, a T test was applied. For frequencies and percentages, a chi-square test was executed. Correlations were analyzed

by Pearson correlation test. $p < 0.05$ showed statistical significance.

RESULTS

Table 1 shows the characteristics of all subjects. Significant difference of BMI and 25 OH D were observed between control and case groups ($p = 0.0001$). Table 2 describes the deficiency and insufficiency of 25 hydroxy D in three types of asthma and in control group. Table 3 shows the relation of 25 hydroxy D with lung functions in control and case groups. It shows that vitamin D had significant relationship with FEV1 and FEV1/FVC in asthmatics ($p = 0.0001$).

DISCUSSION

Vitamin D affects the immune system by its immune-modulatory role.¹⁴ The result of this research revealed that none of the subjects had sufficient levels of this vitamin. A previous Pakistani study also showed that vitamin D insufficiency was very common in all ages in both male and female subjects.¹⁵ In this study, most of the non-asthmatic control individuals having mild and some having moderate insufficiency of this vitamin.

While among cases, no one had mild insufficiency but as the severity of asthmatic state was increased, the levels of VD reduced from moderate insufficiency to severely insufficient or even deficient state. Jat and Khairwa found low VD in asthmatics than controls and detected increase odds of asthma in their asthmatic subjects that had poor serum levels of VD.¹⁶ On the other hand, Maalmi et al, reported a non-significant change in the VD levels of healthy subjects and asthmatic subjects. Though, when they distributed the asthmatics and non-asthmatics with respect to vitamin D classification, obvious differences were seen in the concentration of serum VD.¹⁷ Vitamin D dampens the synthesis of antibodies and inhibits B lymphocyte differentiation into plasma cells. It promotes the anti-inflammatory action of Th2 and Treg cells.¹⁸

VD discriminates CD4 cells into T reg lymphocytes and stimulates its anti-inflammatory actions by the release of IL 10. In asthma, low serum 25(OH)D levels are consistent with less IL 10 released by T reg cells.¹⁹ Korn et al,²⁰ also found that their asthmatic cases and control groups had deficiency of this vitamin. Similarly, they also observed that there was a gradual lower level of VD when severity of asthma increased. Previous studies found that vitamin D is strongly related with inflammatory diseases like asthma, Crohn's disease and ulcerative colitis.²¹

A previous study detected that any alteration in the VDR gene may lead to asthma. VDR is a nuclear receptor with a strong affinity for VD resulting in the production of transporters like calbindin which enhances calcium

reabsorption from intestinal epithelial cells. Intracrine signaling by VDR is facilitated in many tissues, for example prostate, placental tissues, dermal cells.²²

In this research work, relationship between VD and lung functions indicated that FEV1 and FEV1/FVC showed positive correlation with vitamin D with significant p values while FVC was not significant. Somashekar et al, compared these pulmonary functions with vitamin D and found reduction of lung functions in asthmatic subjects.²³

CONCLUSION

Vitamin D has pronounced effects on asthmatic condition by its immuno-modulatory functions. Routine examination of serum vitamin D in asthmatics may be helpful for indicative and prognostic purposes. Multiple clinical trials should be conducted by giving vitamin D supplements to asthmatic patients to see its therapeutic effectiveness in this disease.

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REFERENCES

- Hall SC, Fischer KD, Agrawal DK. The impact of vitamin D on asthmatic human airway smooth muscle. *Exp Rev Respir Med* 2016;10:127-35.
- Sabar MF, Akram M, Awan, FI, Ghani MU, Shahid, M, Iqbal Z, et al. Awareness of Asthma Genetics in Pakistan: A Review with Some Recommendations. *Adv Life Sci* 2018;6:1-10
- To T, Stanojevic S, Moores G, Gershon AS, Bateman ED, Cruz A, et al. Global asthma prevalence in adults: findings from the cross-sectional world health survey. *BMC Public Health* 2012;12:204.
- Holick MF. The vitamin D deficiency pandemic: Approaches for diagnosis, treatment and prevention. *Rev Endocr Metab Disord* 2017;18:153-65.
- Tommola M, Ilmarinen P, Tuomisto LE, Haanpää J, Kankaanranta T, Niemelä O, et al. The effect of smoking on lung function: a clinical study of adult-onset asthma. *Eur Respir J* 2016;48:1298-306.
- Jiménez-Sousa MÁ, Martínez I, Medrano LM, Fernández-

- Rodríguez A, Resino S. Vitamin D in human immunodeficiency virus infection: influence on immunity and disease. *Front Immunol* 2018;9:458.
7. DeLuca HF. History of the discovery of vitamin D and its active metabolites. *Bone Key Rep* 2014;3:479-85.
 8. Liu NQ, Hewison M. Vitamin D, the placenta and pregnancy. *Arch Biochem Bio Phy* 2012;523:37-47.
 9. Coussens AK. The role of UV radiation and vitamin D in the seasonality and outcomes of infectious disease. *Photochem Photobiol Sci* 2017;16:314-38.
 10. Lang PO, Aspinall R. Vitamin D status and the host resistance to infections: what it is currently (not) understood. *Clin Ther* 2017;39:930-45.
 11. Gruber-Bzura BM. Vitamin D and influenza—prevention or therapy? *Int J Mol Sci* 2018;19:2419.
 12. Greiller CL, Martineau AR. Modulation of the immune response to respiratory viruses by vitamin D. *Nutrients* 2015;7:4240-70.
 13. Global Initiative for Asthma. GINA report, global strategy for asthma management and prevention. <http://www.ginasthma.org>. 2019
 14. Gombart AF, Pierre A, Maggini S. A review of micronutrients and the immune system—working in harmony to reduce the risk of infection. *Nutrients* 2020;12:236-9.
 15. Masood, Z., Mahmood, Q, Ashraf, K.T. Vitamin D deficiency—an emerging public health problem in Pakistan. *J Univ Med Dent Coll* 2010;1:1-9.
 16. Jat KR, Khairwa A. Vitamin D and asthma in children: A systematic review and meta-analysis of observational studies. *Lung India* 2017;34:355-9.
 17. Maalmi H, Berraïes A, Tangour E, Ammar J, Abid H, Hamzaoui K, et al. The impact of vitamin D deficiency on immune T cells in asthmatic children: a case-control study. *J Asthma Allergy* 2012;5:11-6.
 18. Watkins J. Preventing a covid-19 pandemic. *British Medical Journal Publishing Group* 2020.
 19. Ginde AA, Mansbach JM, Camargo CA. Association between serum 25-hydroxyvitamin D level and upper respiratory tract infection in the Third National Health and Nutrition Examination Survey. *Arch Intern Med* 2009;169:384-90.
 20. Korn, S, Hübner M, Jung M, Blettner M, Buhl R. Severe and uncontrolled adult asthma is associated with vitamin D insufficiency and deficiency. *Respir Res* 2013;14:25-9.
 21. Han JC, Du J, Zhang YJ, Qi GB, Li HB., Zhang YJ. Vitamin D receptor polymorphisms may contribute to asthma risk. *J Asthma* 2016;53:790-800.
 22. Chambers ES, Suwannasaen D, Mann EH, Urry Z, Richards DF, Lertmemongkolchai G, et al. 1α , 25-dihydroxyvitamin D3 in combination with transforming growth factor- β increases the frequency of Foxp3+ regulatory T cells through preferential expansion and usage of interleukin-2. *Immunology* 2014;143:52-60.
 23. Somashekar AR., Prithvi AB, Gowda M.N. Vitamin D Levels in Children with Bronchial Asthma. *J Clin Diagn Res* 2014;8:4-7.

Systemic immune inflammation index - an emerging marker for rheumatoid arthritis disease activity

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Objective: To determine the association of systemic immune inflammation index with DAS 28ESR (disease activity score) for rheumatoid arthritis and its value as an emerging biochemical marker for rheumatoid arthritis disease activity.

Methodology: This retrospective cross-sectional study was performed at the rheumatology unit of Federal Government Polyclinic Hospital, Islamabad from December 2020 to June 2021. A total of 290 rheumatoid arthritis patients' data was analyzed. DAS 28 ESR was computed using the DAS 28 ESR calculator and the systemic immune inflammation index (SII) was obtained by the equation platelet count x neutrophil count/lymphocyte count. Data were analyzed using several parametric and nonparametric tests on the SPSS version 23.

Results: Out of 238 patients, 186(82.1%) were females

and 52 (17.9%) males. Mean age was 45.2 ± 12 years. DAS28 ESR score showed disease activity as 8.9% in remission, while 10% had low disease activity, 55.9 % had moderate activity, and 25.2% had high disease activity. Mean SII with DAS 28 ESR ≤ 3.2 was 673.85 ± 433.74 while patients showing moderate to high disease activity (DAS 28 ESR ≥ 3.2) exhibited an SII of 1005.46 ± 607.6 . Advanced statistical tests showed this to be a significant finding [spearman's correlation analysis ($p=0.000$)].

Conclusion: SII was found to be a reliable, cheap, and easily available index for measuring status of disease in patients with rheumatoid arthritis.

Key Words: Rheumatoid Arthritis, systemic immune inflammation index (SII), disease activity score ESR (DAS 28).

INTRODUCTION

Rheumatoid arthritis (RA) is the commonest autoimmune disorder encountered in rheumatology clinics as well as in the physician's practice either as its first presentation or with an extra-articular manifestation. It can be seen as an incendiary disease capable of causing destruction of the joints and their surrounding structures, with the potential of causing severe and disabling extra-articular manifestations, a reduced number of years, and compromised quality of life (QoL).¹

The hallmark of this disease is inflammation and it is assessed to measure the long-term outcome. In busy rheumatology clinics, sedimentation rate of the red blood cells termed as ESR and C-reactive protein (CRP) are routinely employed to measure the disease's status in terms of inflammation.² Sometimes, both these indices are incorporated into complex mathematical formulae to get an in-depth idea about the disease. One such example is Disease Activity Score, DAS28ESR/CRP, which is widely used as a severity index to monitor the disease and modify treatment accordingly.

It has also been noted consistently that systemic inflammation leads to certain shifts in circulating blood cells both in their number as well as in composition. A few commonly noticed features in patients suffering from

chronic inflammatory conditions are normochromic anemia, thrombocytosis, lymphopenia, and neutrophilia. Therefore, for the assessment of inflammatory activity, these changes can be used in conditions like RA.³ The advantage of these inflammatory markers is that they can easily be obtained from a simple blood complete picture test and that this simple test is available in even the remotest areas. Therefore, the discovery of new biomarkers in RA can aid in more effective comprehension of the disease at different stages and its activity.⁴

Some of the newer indices of inflammation that have been studied in various autoimmune disorders include different ratios of the blood cells like the ratio of neutrophils to lymphocytes termed as (NLR), ratio of platelets to lymphocytes (PLR) and the volume of the platelets like (MPV) and width of the red blood cells distribution in terms of the mean corpuscular volumes (RDW). These have been studied in different inflammatory arthritides, SLE and various malignancies. Systemic immune inflammation index (SII) is a new addition to the list which is capable of pointing towards the presence of inflammation more precisely than PLR or NLR alone but has not been studied extensively in rheumatological disorders.⁵⁻⁷ It was first utilized in 2014

in assessing the inflammatory index in hepatocellular carcinoma but since then it has been utilized more in the assessment of different types of malignancies like renal cell carcinoma, breast cancer, mesotheliomas, lung cancer, esophageal and cervical cancers in particular.^{8,9} Few studies have also noted its significance in determining the disease activity in ANCA-associated vasculitis and those suffering from ankylosing spondylitis.¹⁰ However, there have been only two studies so far in RA patients using this marker. Hence, we aimed to assess its utility in RA patients and ascertain its association with the status of their disease in our tertiary care setup.

METHODOLOGY

This study was conducted retrospectively in the Rheumatology unit of Federal Government Polyclinic Hospital, Islamabad. The approval from the Ethical Review Board of Postgraduate Medical Institute (Ref No. FGPC. 1/12/2023/ethical committee dated March 26, 2023) was obtained. The WHO sample size calculator was employed to compute the required sample size for the study. The confidence interval was kept at 95% and the margin of error at 5%.

All patients who fulfilled the classification criteria for RA set by the EULAR/ACR in 2010 were included in the study. Patients with any concurrent illness that could affect SII were excluded from the study like for example

coronary heart disease, renal failure, hypertension, diabetes, hematologic or solid organ malignancies, any infections, or patients in peripartum period.

DAS 28 ESR SCORE/DAS 28 SCORE was employed to gauge the disease activity of the participants. It takes into consideration the swelling and tenderness of 28 joints of the body that include the proximal interphalangeal joints, metacarpophalangeal joints, wrist, elbow, and shoulder joints bilaterally in the upper limbs, however, in the lower limbs only knees are included. Along with the joints, the patient's global health on a scale of 0 to 100 mm and fresh ESR of the patient are also needed. These values are then put in the formula to get the final score.

Depending upon their score, the patients are classified into different disease activity categories as follows; patients with a score of <2.6 signifies disease remission, a score between 2.6-3.2 denotes a mild disease activity, moderate disease activity has a score between 3.2-5.1 and anything >5.1 shows high disease activity.

Systemic immune inflammation index (SII) was studied and the following formula is used to calculate it; **Platelets count x neutrophil count/lymphocyte count.**¹¹

Statistical Analysis: The data were analyzed using the IBM SPSS version 23. SII and DAS 28 ESR scores for each patient were calculated. To test if DAS28-ESR score of the participants was associated with the value of SII, Chi square test was utilized. Spearman correlation

analysis was done to find the significance and strength of the relationship between abnormally distributed data among groups. Mann Whitney U test was done for various variables and receiver operator curves (ROC) were generated for finding the sensitivities in particular for SII in comparison to ESR. A p-value $\leq .05$ was considered statistically significant.

RESULTS

The study involved 290 patients in total; 238 (82.1%) females and 52 (17.9%) males with a mean age of 45.2±12 years. Of the 290 participants, 8.9% were in remission of disease, 10%

Table 1: Baseline Demographics of the study population.

Variable	Minimum	Maximum	Mean±SD
Age (years)	16	75	45.02 ± 12.5
DAS28-ESR	1.20	8.34	4.29895 ± 1.26
ESR (mm/hr)	5	110	33.75 ± 20.6
WBC (4000-11000/mm ³)	3700	16510	8630.48 ± 2342.45
Hemoglobin(g/dl)	9.50	16.60	12.41 ± 1.38
Platelets (150,000-400,000/mm ³)	120000	651000	310620.83 ± 99183.17
Neutrophils (40-70%)	40.00	87.0	66.84 ± 9.03
Lymphocytes (20-40%)	1.7	48.00	25.96 ± 8.10
Systemic immune inflammation index	142.32	3830.70	929.99±588.72

had low disease activity, 55.9% had moderate activity, and 25.2% had high disease activity based on the DAS28 ESR score (Fig. 1). Demographic traits of the participants are given in Table 1. Mean SII in patients with RA having DAS 28 ESR ≤ 3.2 (low disease activity and disease remission) was 673.85 ± 433.74 while those with moderate to high RA disease activity i.e. DAS 28 ESR ≥ 3.2 (moderate and high disease activity) had an SII of 1005.46 ± 607.6 . This was statistically significant on spearman's correlation analysis ($p=0.000$). Mann Whitney U test results are shown in Table 2.

Receiver operator curve as

Table 2: Comparison of characteristics in patients with inactive and active RA.

Variable	Inactive RA (low and remission)	Active RA (moderate to high das28)	p value
Age, years+	43.29 $\pm$ 10.91	45.53 $\pm$ 12.90	
ESR (mm/h)	22.35 $\pm$ 12.50	37.62 $\pm$ 20.96	0.000 ^a
WBC	8214.39 $\pm$ 2094.31	8753.08 $\pm$ 2401.29	0.122
Neutrophil %	61.69 $\pm$ 10.15	68.41 $\pm$ 8.01	0.000 ^a
Lymphocyte%	31.12 $\pm$ 8.04	24.50 $\pm$ 7.35	0.000 ^a
DAS28 ESR	2.63 $\pm$ 0.54	4.74 $\pm$ 0.96	
Platelet count	292335.45 $\pm$ 90113.5	316008.48 $\pm$ 101260.7	0.153
NLR	2.25 $\pm$ 1.22	3.13 $\pm$ 1.31	0.000 ^a
SII	673.85 $\pm$ 433.74	1005.46 $\pm$ 607.6	0.000^a
N (%)	66(22.76%)	224(77.24%)	

Mann Whitney U test^a

Fig 1- Disease activity categories based on DAS 28ESR score.

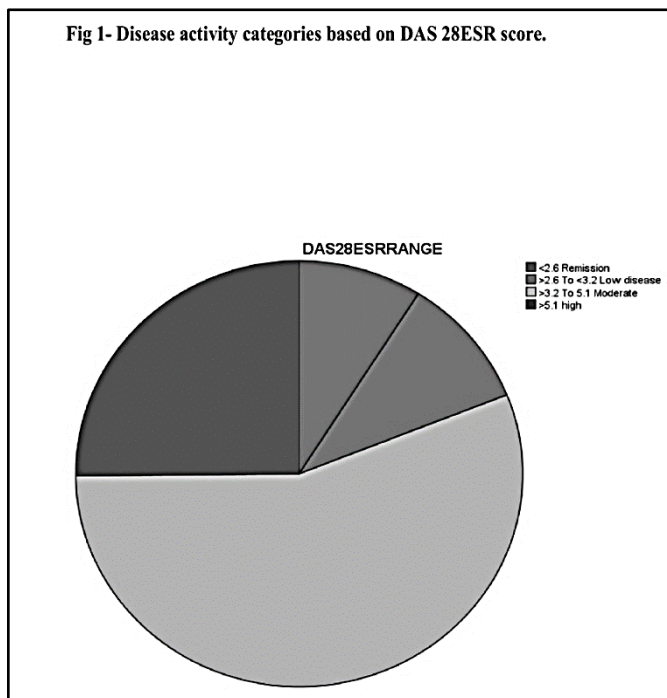
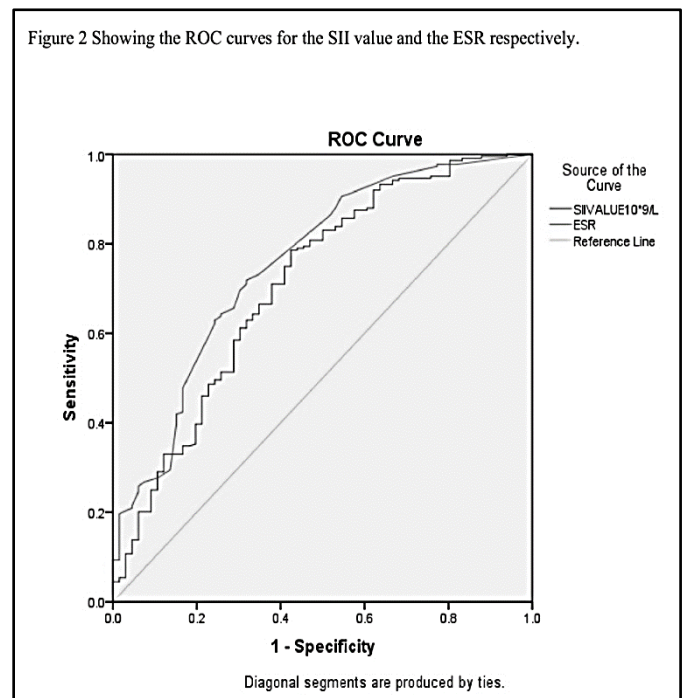


Figure 2 Showing the ROC curves for the SII value and the ESR respectively.



illustrated in Figure 2 for SII and ESR were comparable, the AUC for SII was 0.71 (CI:95 %, 0.635-0.786, $p<0.001$) and for ESR AUC was 0.756 (CI:95% 0.687-0.824, $p<0.001$). The maximum sensitivity of SII was 78.6% while that for ESR was 82.4% for the severity of disease in terms of DAS-28ESR score. The sensitivity of SII was almost comparable to that of ESR but specificity is low as can be seen in the ROC curves.

DISCUSSION

Changes in the different parameters in the blood of the patients like an increase in neutrophils, platelets, lymphocytes, monocytes, and changes in the red cell distribution width are seen in many inflammatory and malignant diseases and RA is no exception.¹² All these entities separately or combined into different systemic inflammatory scores are being studied in these conditions as a pointer of disease activity with the added value of

being cheap and easily available.^{13,14} The reason of doing our study was to find the role of SII in RA patients and its correlation with disease activity. Very few studies have been done on this topic and so far none have been conducted in Pakistan as yet.

The results of our study verified the finding that SII is higher in cases with higher disease activity and vice versa. It was seen to be statistically significant on Spearman's correlation analysis and the Mann-Whitney U test ($p=0.000$). A review of the literature showed that the same observation was reported by Satis in Turkey with a significance of 0.030.¹⁵ Yoshikawa et al, reported a mean SII of 513.6 in the remission group, 605.7 in low disease group 793.8 in moderate disease activity group, and 1367.1 in the high disease activity group. Furthermore, they also reported that SII had better relationship with disease activity than the previously studied index Neutrophil to Lymphocyte Ratio (NLR).¹⁶ SII in other rheumatological disorders like ankylosing spondylitis has also been correlated with disease activity like in a study done by Wu et al, from China.⁷ Studies have been published recently on its utility as a novel biomarker in psoriatic arthritis as well.¹⁷ Conversely, one study done in Baltimore did not show any correlation between the hematological parameters and the disease activity of RA patients.¹⁸

A further literature search revealed that SII has been studied in some chronic conditions causing vasculitis as well. Examples include a publication by Tanacan et al, on patients with Behçet syndrome (BS) who exhibited higher values of SII if their disease was uncontrolled¹⁹ as was observed by Chen et al and Kim et al, in patients having ANCA-associated vasculitis i.e. those having higher SII values had higher vasculitis disease activity and a poorer prognosis.^{20,21} All these studies support the fact that diseases with chronic inflammation lead to changes in the neutrophil, lymphocytes, and platelets and thus higher value of SII and show a correlation with the disease activities assessed by different scores.

This parameter can also be used to monitor the treatment response i.e. decrease in the score from baseline in response to different treatment modalities. This aspect has been evaluated in a recent study by Gezer and Pehlivan from Turkey which found a significant ($p<0.05$) change in the inflammatory parameters like NLR, SII, CRP, PLR and ESR from the baseline value at the initiation of biological or targeted synthetic DMARDs to the assessment done at 6 months of treatment.

This study is the first one of its kind in Pakistan and it fulfilled its aim to refute the idea that there is no correlation between the SII and DAS28 ESR for the RA disease activity. On the contrary, it correlated very well with it.

The study had a few limitations; for instance, the study was done retrospectively and a one-time assessment was done for the value of SII and it was not followed prospectively. The DMARDs that the patients were taking i.e. conventional synthetic or biologic agents, were not taken into account while doing the evaluation. So, for future research purposes, a prospective study and the influence of different DMARDs on SII and other inflammatory hematological parameters can be studied.

CONCLUSION

The systemic Immune Inflammation Index can be used as an inexpensive and easily available marker for the assessment of disease severity in patients ailing with rheumatoid arthritis.

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REFERENCES

1. Kugyelka R, Kohl Z, Olasz K, Mikecz K, Rauch TA, Glant TT, et al. Enigma of IL-17 and Th17 cells in rheumatoid arthritis and in autoimmune animal models of arthritis. Mediators of inflammation. Volume 2016, Article ID 6145810, 11 pages.
<http://dx.doi.org/10.1155/2016/6145810>
2. Hobbs KF, Cohen MD. Rheumatoid arthritis disease measurement: a new old idea. Rheumatology 2012;51(suppl_6):vi21-7.
3. Kisacik B, Tufan A, Kalyoncu U, Karadag O, Akdogan A, Ozturk MA, et al. Mean platelet volume (MPV) as an inflammatory marker in ankylosing spondylitis and rheumatoid arthritis. Joint Bone Spine 2008;75:291-4.
4. Gavrilă BI, Ciofu C, Stoica V. Biomarkers in rheumatoid arthritis, what is new? J Med Life 2016;9:144-9.
5. Hao X, Li D, Wu D, Zhang N. The relationship between hematological indices and autoimmune rheumatic diseases (ARDs), a meta-analysis. Scientific Rep 2017;7:1-9.
6. Yang Z, Zhang Z, Lin F, Ren Y, Liu D, Zhong R, et al. Comparisons of neutrophil-, monocyte-, eosinophil-, and basophil-lymphocyte ratios among various systemic autoimmune rheumatic diseases. J Pathol Microbiol Immunol 2017;125(10):863-71.
7. Wu J, Yan L, Chai K. Systemic immune-inflammation index is associated with disease activity in patients with

- ankylosing spondylitis. *J Clin Laboratory Analysis* 2021;35(9):e23964.
8. Hu B, Yang X-R, Xu Y, Sun Y-F, Sun C, Guo W, et al. Systemic immune-inflammation index predicts prognosis of patients after curative resection for hepatocellular carcinoma. *Clin Cancer Res* 2014;20:6212-22.
 9. Dong M, Shi Y, Yang J, Zhou Q, Lian Y, Wang D, et al. Prognostic and clinicopathological significance of systemic immune-inflammation index in colorectal cancer: a meta-analysis. *Ther Adv Medical Oncol* 2020;12:1758835920937425.
 10. Huang Y, Gao Y, Wu Y, Lin H. Prognostic value of systemic immune-inflammation index in patients with urologic cancers: a meta-analysis. *Cancer Cell Int* 2020;20:1-8.
 11. Kim JW, Jung JY, Suh CH, Kim HA. Systemic immune-inflammation index combined with ferritin can serve as a reliable assessment score for adult-onset Still's disease. *Clin Rheumatol* 2021;40:661-8.
 12. Olumuyiwa-Akeredolu OO, Pretorius E. Platelet and red blood cell interactions and their role in rheumatoid arthritis. *Rheumatol Int* 2015;35:1955-64.
 13. Yang R, Chang Q, Meng X, Gao N, Wang W. Prognostic value of systemic immune-inflammation index in cancer: a meta-analysis. *J Cancer* 2018;9:3295-8.
 14. Yorulmaz A, Hayran Y, Akpinar UM, Yalcin BA. Systemic immune-inflammation index (SII) predicts increased severity in psoriasis and psoriatic arthritis. *Curr Health Sci J* 2020 ;46:352-7.
 15. Satis S. New Inflammatory Marker Associated with Disease Activity in Rheumatoid Arthritis: The Systemic Immune-Inflammation Index. *Curr Health Sci J* 2021;47:553-8.
 16. Yoshikawa T, Furukawa T, Tamura M, Hashimoto T, Morimoto M, Azuma N, et al. systemic immune-inflammation index in rheumatoid arthritis patients: relation to disease activity. *Ann Rheumatol Dis* 2019. Abstract No THU0106.
 17. Dincer AB, Sezer S. Systemic Immune Inflammation Index as a Reliable Disease Activity Marker in Psoriatic Arthritis. *J Coll Physicians Surg Pak* 2022;32:773-8.
 18. Erre GL, Buscetta G, Mangoni AA, Castagna F, Paliogiannis P, Oggiano M, et al. Diagnostic accuracy of different blood cells-derived indexes in rheumatoid arthritis: A cross-sectional study. *Medicine* 2020;99:(44):e22557.
 19. Tanacan E, Dinçer D, Erdogan FG, Gurler A. A cutoff value for the Systemic Immune-Inflammation Index in determining activity of Behçet disease. *Clin Experimental Dermatol* 2021;46:286-91.
 20. Chen JB, Tang R, Zhong Y, Zhou YO, Zuo X, Luo H, et al. Systemic immune-inflammation index predicts a reduced risk of end-stage renal disease in Chinese patients with myeloperoxidase-anti-neutrophil cytoplasmic antibody-associated vasculitis: A retrospective observational study. *Experimental and Therapeutic Medicine* 2021;22:1-6.
 21. Kim Y, Choi H, Jung SM, Song JJ, Park YB, Lee SW. Systemic immune-inflammation index could estimate the cross-sectional high activity and the poor outcomes in immunosuppressive drug-naïve patients with antineutrophil cytoplasmic antibody-associated vasculitis. *Nephrology* 2019;24:711-7.
 22. Gezer Hh, Pehlivan O. Systemic immune-inflammation index and other inflammatory parameters in patients receiving biological or targeted synthetic DMARDs for inflammatory rheumatic disease. *Marmara Med J* 2022;35:316-22.

Prevalence of osteoarthritis in Nawab Shah, Pakistan: A cross-sectional study

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Objective: To determine the prevalence of osteoarthritis and its relationships to dietary practices, socioeconomic position, demographic traits, and educational attainment at Peoples Medical Hospital, Nawabshah.

Methodology: A total of 480 individuals were included in this cross-sectional study. Eligible participants were individuals aged 18-85 years of both genders and residing in Nawab Shah. Individuals with severe illness were excluded. The demographic information, education level, socioeconomic status, and eating habits were recorded. Chi-square tests were used for the analysis of the results.

Results: Participants in the study area had an 18.13%

(n=87) prevalence of osteoarthritis. The prevalence was higher in rural regions (70.11%) than in urban regions (29.89%). Osteoarthritis prevalence was significantly correlated ($p=0.003$) with age and socioeconomic status ($p=0.004$). There was a significant correlation between poor nutrition and a decreased intake of milk with osteoarthritis.

Conclusion: Prevalence of osteoarthritis was 18.13% in Nawab Shah, with higher rates in rural areas (70.11%). While age and socioeconomic status showed correlations, caution is needed in generalizing gender and dietary impacts.

Keywords: Arthritis, nutrition, osteoarthritis, socioeconomic status.

INTRODUCTION

Osteoarthritis, affects millions worldwide, significantly impacting individuals' lives and straining healthcare systems.¹ In Nawabshah, Pakistan, as in many places, the burden of arthritis is evident, with osteoarthritis and rheumatoid arthritis being common among over 100 joint disorders, affecting people of all ages and backgrounds.^{2,3} Regional and demographic factors have a significant global impact on the prevalence of osteoarthritis.^{3,4}

The frequency of osteoarthritis is higher in South Asia due to its aging population, despite lifestyle choices, genetics, and treatment availability.² Understanding the unique combination of cultural, environmental, and economic factors in Nawabshah, a city in central Pakistan, is crucial. The actual prevalence of osteoarthritis in Nawab shah is still not known. Local cultural and dietary practices can significantly influence osteoarthritis prevalence, with specific foods and spices affecting symptoms.^{5,6}

Healthcare outcomes and access are frequently correlated with socioeconomic status.⁷⁻⁹ Understanding the regional incidence and risk factors for osteoarthritis in Nawabshah is not simply of academic interest; it also has practical consequences for the organization and delivery of healthcare services.^{7,8} Authorities can more effectively deploy resources where they are most needed by being aware of the incidence of osteoarthritis^{10,11}

The management frequently entails a lifestyle change. The burden of osteoarthritis can be lessened by identifying modifiable risk factors and putting preventative measures in place, enhancing community health and well-being in the process.¹²⁻¹⁴ The aim of this study was to determine the prevalence of osteoarthritis and its relationships to dietary practices, socioeconomic position, demographic traits, and educational attainment in Nawabshah.

METHODOLOGY

This cross-sectional study was carried out at Peoples University of Medical & Health Sciences for Women (PUMHSW) from August 2022 to August 2023. A random sampling method ensured representation from urban and rural areas, resulting in a sample size of 480 individuals aged 18-85. Excluded were those below 18 or above 85, living outside Nawabshah, or unable to provide informed consent due to cognitive impairment or illness. The study was approved by PUMHSW review committee (Ref: PUMHSW/SBA/PVC/ERC/2023/308 dated September 26, 2023) and all participant provided their consent.

Data were collected through a questionnaire covering demographics, education, socioeconomic status, dietary habits, and uric acid levels.

Statistical Analysis: Data were analyzed by SPSS

version 22. chi-square tests identified associations between variables. $p < 0.05$ was considered significant.

RESULTS

The study involved 480 participants with a nearly equal gender distribution (244 males and 236 females). The ages ranged from 18 to 85 years (mean 42.67 ± 23.41). Most of the participants, 60.63% ($n=291$), resided in rural areas. The educational background showed that majority were illiterate or had primary education. In terms of socioeconomic status, 51.25% ($n=246$) were categorized as having a poor income (5000–20,000 rupees/month), 30.21% ($n=145$) fell into the middle-income category (20,000–50,000 Rs/month), and 18.54% ($n=89$) had an upper income (>50,000 Rs/month) (Table 1).

Table 1: Demographic characteristics of study population ($n=480$).

Demographic		%	Number
Gender	Male	50.83	244
	Female	49.17	236
Residential area	Rural	60.63	291
	Urban	39.37	189
Education	Illiterate	30.83	148
	Primary education	27.92	134
	Middle Education	23.13	111
	Graduates	11.87	57
	Higher education	6.25	30
Socioeconomic status	Poor income	30.21	145
	Middle income	51.25	246
	Upper income	18.54	89

Participants had an 18.13% ($n=87$) prevalence of osteoarthritis (Table 2). Chi-square tests exhibited a significant association ($p=0.003$) between osteoarthritis prevalence and age, with a higher prevalence in older age groups. Educational level did not present a significant association ($p=0.06$) with the prevalence of osteoarthritis. There was a significant association ($p=0.004$) between osteoarthritis prevalence and socioeconomic status, with a higher prevalence among participants in the poor

income category. Participants with poor dietary habits and lower milk consumption had a higher prevalence ($p=0.002$) of osteoarthritis (Table 3).

Table 2: Prevalence of osteoarthritis.

Prevalence of Osteoarthritis		%	Number
Total participants with osteoarthritis		18.13	87
Gender	Male	39.08	34
	Female	60.92	53
Residential area	Rural	70.11	61
	Urban	29.89	26

Table 3: Dietary habits and uric acid levels.

Dietary Habits and Uric Acid Levels		%	Number
Dietary habitat	Daily milk consumption	30	144
Weekly meal quality	Poor	64.58	310
	Good	25.21	121
	Extraordinary	10.21	49
Uric acid level	<2.4 mg/dL	7.91	38
	2.4-6.0mg/dL	39.38	189
	6.0-7.0 mg/dL	34.58	166
	>7.0 mg/dL	18.13	87

DISCUSSION

The study observed a fairly equal distribution of gender among participants, with slightly more males (50.83%) than females (49.17%). Osteoarthritis prevalence was found to be higher among females, consistent with previous studies.^{1,6} The rural-urban divide in the study revealed that osteoarthritis was more prevalent in rural areas (70.11%) compared to urban areas (29.89%), which is in line with studies showing higher osteoarthritis rates in rural populations.^{8,10}

The educational levels of the participants varied, with a substantial proportion of illiterate (30.83%) and just somewhat educated (27.92%) individuals. It's crucial to emphasize that osteoarthritis is a disease that may affect people of all educational levels, even if the study did not find a statistically significant association between educational attainment and the prevalence of osteoarthritis ($p=0.06$).¹² Future studies could delve

deeper into these aspects to elucidate their role in osteoarthritis dynamics.

A significant relationship between osteoarthritis prevalence and socioeconomic status was found ($p=0.004$), with a higher incidence among those in the low-income category (30.21%). This is consistent with past research that has linked a lower socioeconomic status with a higher chance of developing osteoarthritis.^{5,8} Poor eating habits and a low milk intake were found to increase the prevalence of osteoarthritis ($p=0.002$). Poor eating habits and low calcium intake have been related to an increase in the prevalence of osteoarthritis and joint problems.¹³ The importance of a balanced diet for avoiding osteoarthritis is shown by this. A substantial majority of participants (39.38%) had uric acid values between the 2.4-6.0 mg/dL range. Elevated uric acid levels have been linked to gout. Even though uric acid levels aren't the focus of this study, it's important to include them when talking about osteoarthritis.⁹

The study identified an 18.13% osteoarthritis prevalence in Nawabshah. Significant associations were observed between osteoarthritis prevalence and age ($p=0.003$) and socioeconomic status ($p=0.004$), indicating that older individuals and those with lower incomes faced a higher risk.¹⁶ These findings provide crucial insights into osteoarthritis frequency and risk factors in Nawabshah. Future studies can delve into the mechanisms underlying these factors and explore treatments to mitigate the disease's impact on the population.

CONCLUSION

Osteoarthritis prevalent in Nawabshah was 18.1%, mostly among women and in rural areas. The identified associations with socioeconomic status and dietary habits highlight the need for tailored interventions and healthcare strategies to address osteoarthritis in this population.

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REFERENCES

1. Keerio NH, Aamir N, Kumar N, Qureshi MA, Saqlain HA, Noor SS. Incidence of writing double NSAIDs in a single prescription for osteoarthritis. *Prof Med J* 2021;28:702-6.
2. Kumar P, Kalpana FN, Khamuani MK, Lohana S, Dembra S, Jahangir M, et al. Frequency of cardiovascular manifestation in patients with rheumatoid arthritis. *Cureus* 2021;13:113-7.
3. Seeran NL, Aamer N, Karim MT, Arain SR, Khan F, Dahani A. Prevalence of Thyroid Dysfunctions in Patients with Rheumatoid Arthritis at Tertiary Care Hospital. *J Dow Univ Health Sci* 2021;15:77-82.
4. Sukharani N, Dev K, Rahul FN, Bai P, Ali A, Avinash FN, et al. Association between rheumatoid arthritis and serum vitamin D levels. *Cureus* 2021;13:108-13.
5. Yarwood A, Huizinga TW, Worthington J: The genetics of rheumatoid arthritis: risk and protection in different stages of the evolution of RA. *Rheumatology* 2016; 55:199-209.
6. Tracy A, Buckley CD, Raza K: Pre-symptomatic autoimmunity in rheumatoid arthritis: when does the disease start? *Sem Immunopathol* 2017;39:423-35.
7. Qvarfordt M, Andersson ML, Larsson I: Factors influencing physical activity in patients with early rheumatoid arthritis: a mixed-methods study. *SAGE Open Med* 2019;7:1-11.
8. Cross M, Smith E, Hoy D, Nolte S, Ackerman I, Fransen M, et al. The global burden of hip and knee osteoarthritis: estimates from the global burden of disease 2010 study. *Ann Rheum Dis* 2014;73:1323-30.
9. Haq SA, Darmawan J, Islam MN, Uddin MZ, Das BB, Rahman F, et al. Prevalence of rheumatic diseases and associated outcomes in rural and urban communities in Bangladesh: a COPCORD study. *J Rheumatol* 2005;32:348-53.
10. Hootman JM, Helmick CG. Projections of US prevalence of arthritis and associated activity limitations. *Arthritis Rheum* 2006;54:226-9.
11. Gabriel SE, Michaud K. Epidemiological studies in incidence, prevalence, mortality, and comorbidity of rheumatic diseases. *Arthritis Res Ther* 2009;11:229-32.
12. Di Giuseppe D, Crippa A, Orsini N, Wolk A. Fish consumption and risk of rheumatoid arthritis: a dose-response meta-analysis. *Arthritis Res Ther* 2014;16:446-9.
13. Choi HK, Mount DB, Reginato AM, et al. Pathogenesis of gout. *Ann Intern Med* 2005;143:499-516.

Effect of oral ondansetron on gastrointestinal transit time when used in combination with oral rehydration therapy in acute gastroenteritis

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Objective: To assess the effect of oral ondansetron on gastrointestinal transit time in acute gastroenteritis and to compare the efficacy of ORS alone and in combination with oral ondansetron in improving oral rehydration in acute gastroenteritis.

Methodology: This comparative analytic study was conducted at Army Medical College in collaboration with pediatric department of Military Hospital, Rawalpindi from January to November 2017. The study included 210 children of age 2-5 years with clinical diagnosis of acute gastroenteritis with mild to moderate dehydration and with at least two episodes of non-bloody loose stools and abdominal pain. All children were randomized into three equal groups with 70 children in each group. Group 1 received only ORS for rehydration, Group 2 received oral ondansetron as single dose at the time of enrollment and after an

interval of 30 minutes, ORT was started as per WHO guidelines and Group 3 received ORS for first 30 minutes and then oral ondansetron. Clinical characteristics were assessed before and after four hours of treatment. Children were assessed after every 30 minutes for the first four hours for the number of episodes of loose stools and abdominal pain.

Results: A significant difference in frequency of stools and abdominal pain was observed between the three groups ($p < 0.001$).

Conclusion: Ondansetron showed a reduction in frequency of loose stools in acute gastroenteritis when used along with ORS leading to quick recovery in children under 5 years of age.

Keywords: Abdominal pain, acute gastroenteritis, gastrointestinal transit time, ondansetron.

INTRODUCTION

Acute gastroenteritis is a common life-threatening illness affecting all age groups. It remains a major cause of malnutrition, morbidity, and mortality in children throughout the world, currently accounting for 0.8 million deaths per year.¹ It is estimated that diarrhea claims the lives of 2.3 million children under the age of five in impoverished nations every single year.² The most affected population is children under the age of five years.

Excessive loss of fluid and electrolytes leads to dehydration and acidosis, which may lead to death. By replacing fluid and electrolytes on time, a greater number of deaths can be prevented.³ In Germany, adults have an annual incidence rate of 0.75 occurrences of acute gastroenteritis on average.² WHO recommends oral dehydration therapy (ORT) with oral rehydration salt (ORS) for mild to moderate dehydration. About 40 years ago, ORS was recommended as a standard therapy for dehydration in acute gastroenteritis.⁴

Mechanical stimulation of the gastrointestinal tract activates vagal afferents but some of these describe this as a direct activation of primary peripheral afferent 5-HT₃ receptors. Ondansetron being a potent 5-HT₃ receptor

antagonist can delay this peristaltic activity.^{5,6} Although ondansetron has an established role as an antiemetic agent,⁷ its effect on gastrointestinal transit time has not been studied in our region. This study is first of its kind to evaluate its role on gastrointestinal transit time showing that ondansetron not only helps to control vomiting but also frequency of loose stools in acute gastroenteritis when used along with ORS leading to quick recovery in children under 5 years of age.

METHODOLOGY

This prospective randomized, single blinded study was conducted in the department of pharmacology in collaboration with pediatrics department of PEMH, Rawalpindi. The study protocol was approved by the Ethical Committee of Army Medical College, Rawalpindi. Parent/guardian gave informed written consent.

The children aged between two to five years, irrespective of gender, were diagnosed with acute gastroenteritis with mild to moderate dehydration labelled by the pediatrician after a brief history and clinical examination. Children with at least two episodes of non-bloody loose stools and abdominal pain were included in the study. WHO Scale

for dehydration for children aged between one month and five year 8 was used. Children with severe dehydration (coma, confusion, edema, convulsions), severe malnutrition, had paralytic ileus, received anti-emetic in the last 24 hours, had IV fluids before enrollment and previous history of cardiac problem were excluded from the study.

Children were randomized into three equal groups with 70 children in each group. Group 1 received only ORS for rehydration at the rate of 75 milliliters per kilograms (ml/kg) body weight in the first four hours with an additional 2ml/kg body weight after each loose stool as per WHO guidelines.⁹ Group 2 received oral ondansetron in a dose of 0.2 mg/kg body weight as single dose at the time of enrollment. After an interval of 30 minutes ORT was started as per WHO guidelines with ORS in dose of 75ml/kg body and continued for up to four hours.¹⁰ Group 3 received ORS as per WHO guidelines for first 30 minutes and then oral ondansetron was given in a dose of 0.2 mg/kg as a single dose. ORT was resumed after an interval of 30 minutes and continued up to four hours.¹¹ Patient's clinical characteristics were assessed before and after four hours of treatment. Children's were assessed after every 30 minutes for the first four hours for the number of episodes of loose stools and abdominal pain. Nine children meeting the inclusion criteria were selected daily and randomized into three groups with three children in each group by the pediatrician. The groups were coded by the pediatrician. The drugs were prescribed by the pediatrician and given by the investigator on random bases without knowing to which group the child belonged and whether the child was receiving ORS or ondansetron. Patients were monitored for the development of known adverse effects.

Assessment of diarrhea/loose stools: None: no episode of loose stools after treatment, Very mild: 1-2 episodes of loose stools after treatment, Mild: 3 episodes of loose stools after treatment, Moderate: 4 episodes of loose stools after treatment, Severe: 5 episodes of loose stools after treatment and Very severe: 6 and above episodes of loose stools after treatment.

Assessment of abdominal pain: Pain was assessed by observing child condition such as crying and leg folding with the severity of pain and by asking from mother. The

Table 1: Demographic characteristics of study population (N=210).

Characteristics	Group 1 (n=70)	Group 2 (n=70)	Group 3 (n=70)
Age (years)	3.11 ± 0.137	2.89 ± 0.137	2.93 ± 0.137
Gender			
Males	49 (70 %)	45 (64.3%)	48(68.6%)
Females	21 (30 %)	25 (35.7%)	22(31.4%)
Weight in kg	13.5 ± 0.44	13.38 ± 0.49	13.08 ± 0.37
Education level of parents (%)			
Illiterate	3 (4.3%)	5 (7.1%)	4 (5.7%)
Primary	19(27.1%)	12(17.1%)	11(15.7%)
Secondary	33(47.1%)	28(40.0%)	32(45.7%)
College/ HSSC	12(17.1%)	19(27.1%)	17(24.3%)
University (bachelors & above)	3 (4.3%)	6 (8.6%)	6 (8.6%)
Number of siblings	1.88 ± 0.117	1.51 ± 0.177	1.75 ± 0.175
Duration of breastfeeding (years)	1.4 ± 0.075	1.0 ± 0.086	1.0 ± 0.072
Age of weaning (months)	5.7 ± 0.162	5.9 ± 0.102	5.8 ± 0.134

scale used to assess abdominal pain was: None: no pain after treatment, Very mild: very mild pain after treatment, Mild: mild pain after treatment, Moderate: moderate pain after treatment, Severe: severe pain after treatment and Very severe: very severe pain after treatment.

Statistical Analysis: Data was analyzed using SPSS version 21. Chi-square test was used to compare variables between the groups. $p < 0.05$ was considered significant.

RESULTS

A total of 210 children were enrolled in the study. Study demographics are shown in Table 1. In group 1, out of 70 children, only one child had no episode of loose stools after the treatment, 24 had moderate, 20 had severe and 6 had very severe episodes of loose stools after treatment. In group 2; 13 children had no episode of loose stools after treatment, 23 had mild, no child showed severe and very severe episodes of loose stools. In group 3; 6 had no episode of loose stools 3 had moderate and no child showed severe and very severe episodes of loose stools. Episodes of loose stools were reduced in 2 and 3 groups after treatment (Table 2, Fig. 1).

In group 1, 3 children had no abdominal pain after the treatment, 24 had mild, and 1 had very severe abdominal

pain. In group 2, 33 children had no abdominal pain, thirty children had very mild, no child showed moderate, severe, and very severe abdominal pain after treatment. In group 3, 33 had no abdominal pain, 35 had very mild and no child showed moderate, severe, and very severe abdominal pain. It was observed that abdominal pain was reduced among group 2 and group 3 children after the treatment (Table 2, Fig. 2). The improvement in abdominal pain between the three groups was statistically significant ($p < 0.001$).

Table 2: Comparison of frequency of loose stools and abdominal pain (N=210).

Study Groups	Episodes of loose stools after treatment							p-value
	None	Very Mild	Mild	Moderate	Severe	Very Severe	Total	
Group 1	1	3	16	24	20	6	70	<0.001
Group 2	13	24	23	10	0	0	70	<0.001
Group 3	6	32	29	3	0	0	70	<0.001
Total	20	59	68	37	20	6	210	
Study Groups	Episodes of Abdominal pain after treatment							p-value
	None	Very Mild	Mild	Moderate	Severe	Very Severe	Total	
Group 1	3	9	24	23	10	1	70	<0.001
Group 2	33	30	7	0	0	0	70	<0.001
Group 3	33	35	2	0	0	0	70	<0.001
Total	69	74	33	23	10	1	210	

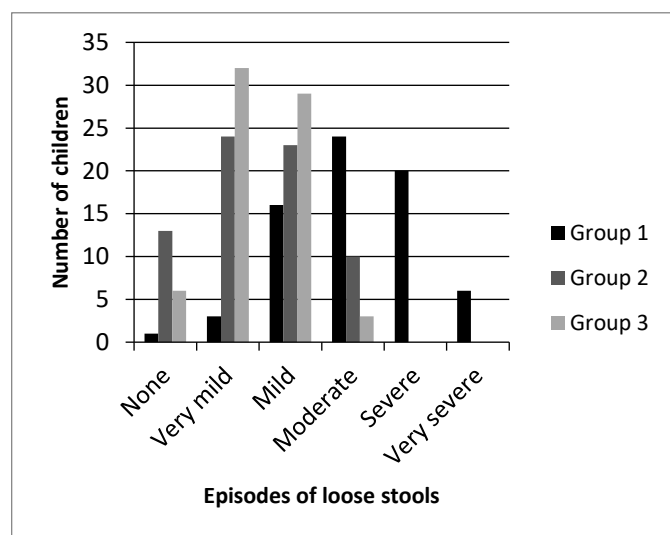


Fig 1: Improvement in frequency of loose stool after treatment.

DISCUSSION

Poor sanitation, unsafe drinking water, low implementation of health care policies are the factors that are increasing the incidence of the diarrhea.¹² Diarrheal diseases ranks as the third cause of mortality among children aged ≤ 5 , with 443,832 mortality cases annually.¹³ Acute gastroenteritis is a major cause of hospitalization worldwide.¹⁴

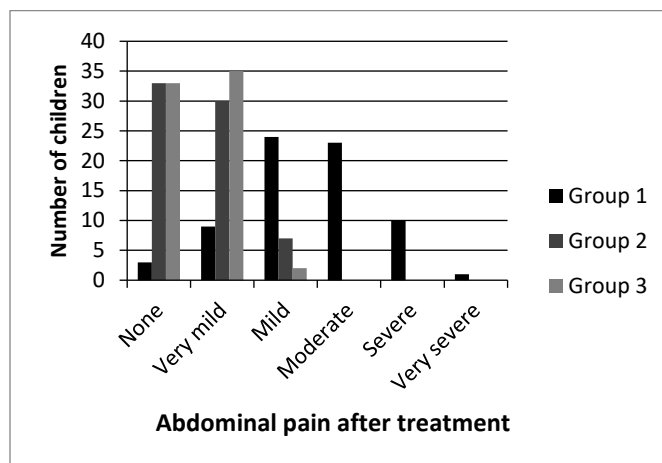


Fig 2: Improvement in abdominal pain after treatment.

As a 5-HT₃ receptor antagonist, ondansetron decreases the pain that is associated with this condition.¹⁵ We found that ondansetron when given orally with ORS as an initial therapy not only reduced vomiting but also loose stools, as shown by another study.¹⁶ Acting peripherally, ondansetron increases the intestinal transit time thereby decreases the stool frequency.¹⁷ ORT is the mainstay of treatment in reducing diarrhea.¹⁸

There has been an exponential increase in the use of intravenous ondansetron in the last few years.¹⁹ According European guidelines, ondansetron is approved to be an effective drug for acute gastroenteritis.¹⁴ In 2016, Marchetti et al conducted a double-blind randomized trial comparing the effect of an oral single dose of ondansetron

in reducing acute gastroenteritis in children and reported that ondansetron reduced the risk of intravenous rehydration by over 50%.²⁰

Our results were consistent with the findings of Hagbom et al, who observed that the frequency of loose stools was reduced after an oral single dose of ondansetron.²¹ Marchetti et al also observed the same effect of ondansetron in their study.²⁰ In an RCT, Gunn et al reported that ondansetron improved stool consistency ($p < 0.001$).²²

Similar findings were reported in a randomized study by Garsed et al, who demonstrated that once daily dosing of ondansetron significantly improved stool consistency response rates in patients.²³ On contrary, a study reported that there was no significant difference in pain intensity after ondansetron treatment.²² While, Plasse et al., demonstrated that mostly patients in ondansetron group had reduced pain after treatment but the findings were not significant.²⁴

CONCLUSION

Our study concluded that ondansetron enhances intestinal transit time, resulting in a reduction in stool frequency. It is suggested from our study that oral ondansetron can be added in treatment regimen of mild to moderate dehydration when ORS alone is not sufficient to control diarrhea.

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REFERENCES

1. Whyte LA, Araj RA, McLoughlin LM. Guidelines for the management of acute gastroenteritis in children in Europe. *Arch Dis Child Educ Pract Ed* 2015;100:308-12.
2. Kumari H, Kumar K, Kumar G, Sharma N. Acute Gastroenteritis: Its Causes, Maintenance, And Treatment. *J Pharm Neg Results* 2022;21:5064-78.
3. Mushtaq A, Khan S, Zeb F, Ain Q, Syed A. Risk Factors Associated with Gastroenteritis in Children 2-5 Years of Age Attending Rehman Medical Institute Peshawar. *Am J Food Sci Health* 2016;2:94-101.
4. Aghsaefard Z, Heidari G, Alizadeh R. Understanding the use of oral rehydration therapy: A narrative review from clinical practice to main recommendations. *Health Sci Rep* 2022;5:e827.
5. Gunn D, Yeldho C, Hoad C, Menys A, Gowland P, Marciani L, et al. Mechanisms underlying the laxative effect of lactulose: A randomized placebo-controlled trial showing increased small bowel water and motility unaltered by the 5-HT₃ receptor antagonist, ondansetron. *Neurogastroenterol Motil* 2024:e14754.
6. Merez K, Hirs M, Biniszewska O, Fichna J, Tarasiuk A. An overview of 5-HT₃ receptor antagonists as a treatment option for irritable bowel syndrome with diarrhea. *Expert Opin Pharmacother* 2023;24:1189-98.
7. Smith C, Smith M, Cunningham R, Davis S. Recent advances in Antiemetics: New formulations of 5-HT₃ Receptor antagonists in adults. *Cancer Nurs* 2020;43:E217-28.
8. Levine AC, Barry MA, Gainey M, Nasrin S, Qu K, Schmid CH, et al. Derivation of the first clinical diagnostic models for dehydration severity in patients over five years with acute diarrhea. *PLoS Negl Trop Dis* 2021;15:e0009266.
9. Kariyappa M. Hyperglycemia, malnutrition, dehydrating gastroenteritis. Hyperglycemia in grade III and grade IV malnutrition with dehydrating gastroenteritis. *JEBMH* 2015;2:4623-9.
10. Danewa AS, Shah D, Batra P, Bhattacharya SK, Gupta P. Oral ondansetron in management of dehydrating diarrhea with vomiting in children aged 3 months to 5 years: A randomized controlled trial. *J Pediatr* 2016;169:105-9.
11. Weghorst AA, Holtman GA, Bonvanie IJ, Wolters PI, Kollen BJ, Vermeulen KM, et al. Cost-effectiveness of oral ondansetron for children with acute gastroenteritis in primary care: a randomised controlled trial. *Br J Gen Pract* 2021;71:e736-43.
12. Qamar K, Nchasi G, Mirha HT, Siddiqui JA, Jahangir K, Shaeen SK, et al. Water sanitation problem in Pakistan: A review on disease prevalence, strategies for treatment and prevention. *Ann Med Surg* 2022;82: Doi: 10.1016/j.amsu.2022.104709.
13. Hasso-Agopsowicz M, Lopman BA, Lanata CF, McQuade ET, Kang G, Prudden HJ, et al. World Health Organization Expert Working Group: Recommendations for assessing morbidity associated with enteric pathogens. *Vaccine* 2021;39:7521-5.
14. Guarino A, Aguilar J, Berkley J, Broekaert I, Vazquez-Frias R, Holtz L, et al. Acute gastroenteritis in children of the world: what needs to be done? *J Pediatr Gastroenterol Nutr* 2020;70:694-701.
15. Bonvanie IJ, Weghorst AA, Holtman GA, Russchen HA, Fickweiler F, Verkade HJ, et al. Oral ondansetron for paediatric gastroenteritis in primary care: a randomised controlled trial. *Br J Gen Pract* 2021;71:e728-35.
16. Leung AK, Hon KL. Pediatrics: how to manage viral gastroenteritis. *Drugs Context*. 2021;10.
17. Rukunuzzaman M, Karim AB, Mazumder W, Nurullah M, Hussain F, Sultana K. Approach to a Child with Irritable Bowel Syndrome: A Review. *J Natl Inst Neurosci Bangladesh* 2017;2:34-9.
18. Ofei SY, Fuchs GJ. Principles and practice of oral

- rehydration. *Curr Gastroenterol Rep* 2019;21:1-6.
19. Fugetto F, Filice E, Biagi C, Pierantoni L, Gori D, Lanari M. Single-dose of ondansetron for vomiting in children and adolescents with acute gastroenteritis—an updated systematic review and meta-analysis. *Eur J Pediatr* 2020;179:1007-16.
20. Marchetti F, Bonati M, Maestro A, Zanon D, Rovere F, Arrighini A, et al. Oral ondansetron versus domperidone for acute gastroenteritis in pediatric emergency departments: Multicenter double blind randomized controlled trial. *PloS One* 2016;11:e0165441.
21. Hagbom M, Novak D, Ekström M, Khalid Y, Andersson M, Lindh M, et al. Ondansetron treatment reduces rotavirus symptoms—A randomized double-blinded placebo-controlled trial. *PloS One* 2017;12:e0186824.
22. Gunn D, Topan R, Barnard L, Fried R, Holloway I, Brindle R, et al. Randomized, placebo-controlled trial and meta-analysis show benefit of ondansetron for irritable bowel syndrome with diarrhoea: the TRITON trial. *Aliment Pharmacol Ther* 2023;57:1258-71.
23. Garsed K, Chernova J, Hastings M, Lam C, Marciani L, Singh G, et al. A randomized trial of ondansetron for the treatment of irritable bowel syndrome with diarrhea. *Gut* 2014;63:1617–25.
24. Plasse TF, Barton G, Davidson E, Abramson D, Kalfus I, Fathi R, et al. Bimodal release ondansetron improves stool consistency and symptomatology in diarrhea-predominant irritable bowel syndrome: a randomized, double-blind, trial. *Am J Gastroenterol* 2020;115:1466-73.

Assessment of testosterone levels among workers exposed to higher workplace temperature versus Controls

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Objective: To assess testosterone levels among workers exposed to higher workplace temperature versus Controls.

Methodology: This cross-sectional descriptive study was done from 01-09-2022 To 02-02-2023 in the Attock city. Group A (Tandoor workers) and Group B (Bankers) each had 81 participants. A structured questionnaire was used to collect demographic, and reproductive health data, while reports of semen analysis and testosterone were recorded on a data sheet developed using MS Excel.

Results: Group A (Tandoor workers) predominantly (46%) belonged to the age group 31-35 years. Of 57% of infertile individuals, 56% were not aware of the cause. In 9% and 12%, sperm motility was active and

sluggish, respectively. 2% of sperm had normal morphology and 19% had zero sperms. Group B (Bankers) (38%) belonged to the age group 31-35 years. 47% of infertile individuals, and out of them, 50% were not aware of the cause. In 5% and 8%, sperm motility was active and sluggish, respectively. 13% of sperm had normal morphology and 23% had zero sperms.

Conclusion: Higher prevalence of infertility was found among tandoor workers in comparison to bankers, primarily because of a higher percentage of sluggish, morphologically abnormal, and dead sperms. There was no significant correlation between workplace temperature, infertility, and sex hormone level.

Keywords: Infertility, Pakistan, pregnancy, diabetes mellitus.

INTRODUCTION

Infertility is labeled if a couple is unable to achieve pregnancy despite regular sexual contact for 2 years. Infertility is also not restricted to a single country, according to the available data this problem has having 15-20% prevalence worldwide.¹ Pakistani population graph is continuously uphill like the overall world population, but infertility prevalence is 21-25% in affected population.²

In Pakistan, unfortunately females are responsible for infertility resulting in verbal, and physical abuse and even marriage contracts ending in divorce.³ Infertility cases have been categorized into several subgroups such as pregnancy never occurred, male and female have normal sperm production and are perfectly healthy but affected by mental stress.⁴ As per previous research based on population demographics, male infertility is twice as compared as females.⁵ Male infertility could be because of multiple causes such as congenital abnormalities, hormonal imbalance, structural anomalies, and chronic diseases) but in 70% of cases, there may be no identifiable cause.^{5,6}

Human anatomy tells us that testes are placed in a small sac (scrotum) outside the human body as sperm production requires a lower temperature as compared to core body temperature.⁷ Scrotum is a thin skin covered with numerous superficial blood vessels that radiate heat to the outer atmosphere thus helping in maintaining a lower temperature.⁸ Males who work in high-temperature areas such as industrial plants (iron, steel, chemical, etc.) and bakeries do face the problem of infertility either complete or delayed achievement of pregnancy as compared to the general population such as office workers like bankers, teachers, etc.⁹ If a person continuously works and remains in high air temperature and radiant heat, in such individuals the process of spermatogenesis may be affected. This study assessed testosterone levels among workers exposed to higher workplace temperature versus control.

METHODOLOGY

This cross-sectional study was conducted from 01-09-2022 To 02-02-2023 in the Attock city area. A total of 84 tandoors were visited and 81 participants fulfilling the

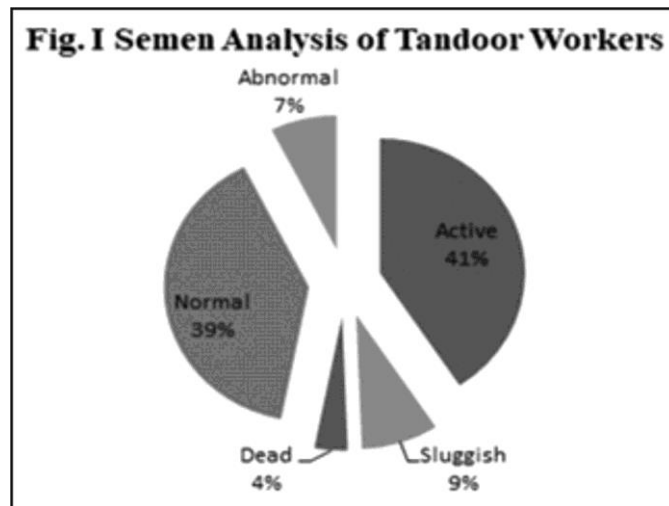
inclusion criteria (age 20 to 40 years and 5 years continuous working at tandoor) were enrolled by simple convenient sampling technique on a volunteer basis after explaining about the study and assured about the confidentiality of data. To remove any selection bias, a control group was created having the same number of participants (81) meeting the inclusion criteria and selected from other professions such as banking.

A structured questionnaire was used to collect demographic and reproductive health data. Temperature recording from the place of work done by using wet globe thermometers. Blood samples for testosterone levels were collected and semen analysis was done on the spot by establishing a mini lab in the Bolon Suzuki Supervised by a trained Pathologist. Semen analysis was only performed for those respondents who did not have a child, and regularly visited their wife to minimize the cost of the study. No fee was charged for the initial clinical examination, and semen analysis.

Statistical Analysis: Data was entered on Excel sheets and analyzed using different statistical tools.

RESULTS

Demographic details and semen analysis of tandoor workers revealed that they predominantly (46%) belonged to the age group 31-35 years, urban background of 69%, 58% must consume snuff and cigarettes, 16% were hypertensive, 2/3 had children (Table 1).



The testosterone levels were found to be within normal limits in both groups A & B except 1 and 3 individuals of groups A & B had low testosterone levels. The correlation between workplace temperature and hormonal under-secretion was proven and was nonsignificant. Group A (tandoor workers) semen analysis results are shown in Fig. 1. In group B, 5% & 8% sperm motility was active and sluggish, respectively. In

13% sperm had normal morphology and 23% had zero sperms, as shown in Fig. 2.

Table 1: Characteristics of tandoor workers (n=81).

Variable	Number	%
Age		
25-30	9	11.11
31-35	38	46.91
36-40	26	32.09
41+	8	9.87
Residence		
Urban	25	30.86
Rural	56	69.13
Social habits		
Nasvar	25	30.86
Smoking	23	28.39
No Addiction	33	40.74
Chronic illness		
DM	7	8.64
HTN	13	16.04
TB	3	3.70
Any Other	6	7.40
Nil	52	64.19
Do you have a child		
Yes	36	42.85
No	48	57.14
If No children, Reason		
Male Infertility	10	20.8
Female Infertility	11	22.91
Don't Know	27	56.25
Work experience		
2 – 3 Years	27	33.33
4 – 5 Years	33	40.74
>5 Years	21	25.92

Demographic details and semen analysis of bankers revealed that they predominantly (38%) belonged to the age group 31-35 years. Urban background of 62%, 64% having of consuming cigarettes. 19% were hypertensive,

47% infertile individuals, and out of them, 50% were not aware of the cause. 39% had work experience of 4 years or more (Table 2).

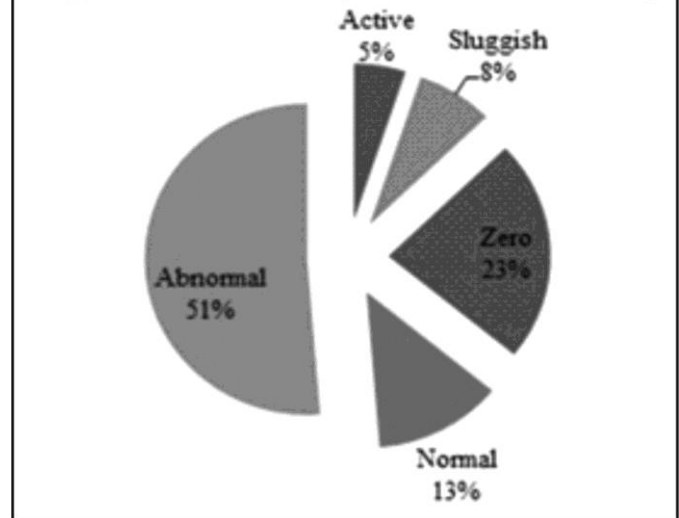
Table 2: Characteristics of control group (bankers) (n=81).

Variable	Number	%
Age		
25-30	23	28.39
31-35	31	38.27
36-40	14	17.28
41+	13	16.04
Residence		
Urban	51	62.96
Rural	30	37.03
Social Habits		
Nasvar	7	8.64
Smoking	52	64.19
No Addiction	22	27.16
Chronic Illness		
DM	12	14.81
HTN	19	23.45
TB	2	2.46
Any Other	9	11.11
Nil	39	48.14
Do You Have a Child		
Yes	43	53.08
No	38	46.91
If No Children, Reason		
Male Infertility	7	18.41
Female Infertility	12	31.57
Don't Know	19	50
Work Experience		
2 – 3 Years	49	60.49
4 – 5 Years	19	23.45
>5 Years	13	16.04

DISCUSSION

Attock, is the last district of Punjab, having a hot humid climate. It is a historic city, established by the British era

Fig. II Semen Analysis Control Group



in the early 19th century. Initially, it was considered a military town, having a very little civilian population.¹⁰ Now the city has become a hub of commercial activities for the agricultural economy having a multi-ethnic population. In recent years there has been rapid population influx from terrorist-affected areas of KPK.^{11,12} With a growing population, multiple restaurants have inbuilt tandoors and solely operative tandoors established to meet the demand for cooked food. More than 150 Tandoors were functional at the time of this study.

In Pakistan, all the research work is mainly based on the population of big urban centers, and less than 1% of is carried out in small cities, or rural areas therefore, it is needed to bring these areas to the limelight, so that research work can be generalized, and problem or issue can be addressed, and solved. There was no previous similar study either in Pakistan or globally.¹³ There are studies based on workers in bakeries, but they are not exactly like our study because in Pakistan the worker is sitting right on the top of the tandoor (as it is placed vertically), whereas in Bakeries the hot oven is placed horizontally, and the workers are standing away from it.¹⁴ A study from Northern Pakistan showed that 15% of the subjects had normal motility and a count of sperm.¹⁵ Our study found 17% of azoospermia while another study from Pakistan reported 13% of azoospermia. Other studies from the USA and Africa also reported similar findings.¹⁶ Our study showed that 33% of cases had structural abnormalities, consistent with other previous research work. In our study, semen analysis of men having no child was done, and it was observed that there was a strong link between high-temperature work environment (Tandoor) leading to increased scrotal temperatures resulting in abnormal sperm production,

motility, and morphology.

These results are in correlation with a study conducted in 2018.¹⁷ In France, a preliminary study was done, selecting volunteers having a successful productive life. They were provided warm underwear for 14-16 hours/daily for 120 days. Semen analyses were done periodically throughout 120 days and continued for the next 180 days. Decreased spermatogenesis was observed; this result is comparable to our study except for sample size and controlled environment (constant temperature maintained).¹⁸

Multiple animal experimental studies have also shown that constant heat exposure regularly results in a devastating effect on sperm production.^{19,20} Multicentric studies are needed to further explore the phenomenon of infertility in detail and generalize the results to the Pakistani population.

CONCLUSION

Higher prevalence of infertility among tandoor workers, primarily because of a higher percentage of sluggish, morphologically abnormal, and dead sperms as compared to the control group. There was no significant correlation between workplace temperature, infertility, and sex hormone level. However, awareness about the causes of infertile individuals in the control group was much more aware of as compared to tandoor workers.

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REFERENCES

- Harris E. Infertility affects 1 in 6 people globally. *JAMA* 2023;329:1443-7.
- Ahmed HM, Khan M, Yasmin F, Jawaid H, Khalid H, Shigri A, et al. Awareness Regarding Causes of Infertility Among Out-patients at a Tertiary Care Hospital in Karachi, Pakistan. *Cureus* 2020;12:e7685.
- Muhammad D, Begum N. Health and social issues of infertile women in Pakistan. *Ann Allied Health Sci* 2018;4:31-2.
- Hayden RP, Flannigan R, Schlegel PN, The role of lifestyle in male infertility: diet, physical activity, and body habitus. *Curr Urol Rep* 2018;19:56.
- Song SH, Kim DS, Yoon TK, Hong JY, Shim SH. Sexual function, and stress level of male partners of infertile couples during the fertile period. *BJU Int* 2016;117:173-6.
- Rooney KL, Domar AD. The relationship between stress and infertility. *Dial Clin Neurosci* 2018;20:41-7.
- Gatimel N, Moreau J, Parinaud J, Léandri RD. Sperm morphology: assessment, pathophysiology, clinical relevance, and state of the art in 2017. *Andrology* 2017;5:845-62.
- Danviboon K, Sripradite S, Tangbumrunkul P, Sangkanjanavanich C, Pruksaseat C, Jeamanukoolkit P, et al. The effects of heat on sperm quality and male infertility: A systematic review. *J Med Health Sci* 2021;28:198-20.
- Gabrielsen J, Tanrikut C. Chronic exposures, and male fertility: the impacts of environment, diet, and drug use on spermatogenesis. *Andrology* 2016;4:648-61. https://attock.punjab.gov.pk/district_profile
- Bardwell H, Iqbal M. The Economic Impact of Terrorism from 2000 to 2018. *Peace Econ Sci Publ Pol* 2021;27:227-61.
- Nasir ZM, Shah SZA, Ahmed H. Cost and benefit analysis of the four China-Pakistan Economic Corridor (CPEC) routs. *Pak Deve Rev* 2017;56:553-60.
- Akhter A. Risk factors analysis for abnormal semen characteristics in sub-fertile males. *Med Today* 2019;31:31-5.
- Hamerezaee M. Assessment of semen quality among workers exposed to heat stress: a cross-sectional study in the steel industry. *Saf Health Work* 2018;99:232-5.
- Khan MS, Deepa F, Ahmed Z. Assessment of male productive health by a conventional method of semen analysis. *J Ayub Med Coll* 2011;23:84-88.
- Khan AA, Khan FA, Sattar A, Naveed AK, Ahmed M. Azoospermia in clinical practice at Rawalpindi. *Pak Armed Force Med J* 1992;42:93-5.
- Shah MA, Imdad L, Ghani S, Humayun F, Rehman QU, Mushtaq S. Correlation Between Occupation and Azoospermia among Industrial Workers in District Faisalabad, Pakistan. *Med Forum Month* 2022;33:81-3.
- Abdelhamid MHM, Esquerre C, Walschaerts M, Ahmad G, Mieusset R, Hamdi S et al. Experimental mild increase in testicular temperature has a drastic but reversible, effect on sperm aneuploidy in men: A pilot study. *Reprod Biol* 2019;19:189-94.
- Silva LKX, Sousa JS, Silva AOA, Junior JB, Faturi C, Martorano LG, et al. Testicular thermoregulation, scrotal surface temperature patterns, and semen quality of water buffalo bulls reared in a tropical climate. *Andrologia* 2018;50. doi.org/10.1111/and.12836
- Setchell B. The effects of heat on the testes of mammals. *Animal Reprod* 2018; 3:81-91.
- Wechalekar H. Effects of whole-body heat on male germ cell development and sperm motility in the laboratory mouse. *Reprod Fert Deve* 2016;28:545-55.

Clinical characteristics of Mpox at a single center in Saudi Arabia: a retrospective study

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Objectives: To describe the clinical characteristics, treatment and outcomes of Mpox as experienced in a tertiary care center in Riyadh, Saudi Arabia.

Methodology: This retrospective study was conducted at King Khalid University Hospital, Riyadh, Saudi Arabia. It included cases seen from May 2022 till the study date. Administrative and electronic medical records were analyzed.

Results: Of 33 patients suspected to have Mpox since May 2022, 16 tested positive. In total, 18.8% patients (3/16) had a personal history of recent travel, and 62.5% (10/16) reported some form of recent sexual contact. All the patients presented with rash, and 93.8% had

anogenital rash. Mean number of skin lesions was 6.69, and no one had coexisting sexually transmitted diseases. Five (31.25%) received antivirals and no mortality was recorded.

Conclusions: All Mpox infections presented with dermatological manifestations. The spread of this disease in our region exhibited some dissimilarities in the clinical presentation and coexisting infections. This highlights the importance of maintaining a high index of suspicion and a low threshold for testing in order to halt further spread.

Keywords: Emergency cases, infectious disease, Monkeypox, Saudi Arabia.

INTRODUCTION

Mpox, previously called monkeypox as introduced by WHO, is a zoonotic viral infection that was first described in humans in the 1970's in the Democratic Republic of Congo.¹ Most cases have been reported from West and Central Africa.² Its spread to the United States was followed by sporadic cases in the United Kingdom, Singapore and Israel.³ WHO declared it a public health emergency of international concern (PHEIC) in July 2022.⁴

The transmission in a recent outbreak was mostly through contact with the skin of an infected person or other areas such as the mouth and genitalia. Transmission through prolonged and close respiratory droplets has also been reported.^{4,5} A confirmed case of Mpox was defined by Saudi Arabian Public Health Agency and the Centers for Disease Control and Prevention (CDC) as a positive polymerase chain reaction (PCR) test for Mpox virus (MPXV) or isolation of MPXV in a culture from a clinical specimen.^{6,7} CDC suspected case definition was a new rash that is characteristic of Mpox.⁷

The most common clinical feature is rash on multiple areas of the body including anogenital area, face and

other parts of the body, along with other symptoms that are less specific like fever, fatigue, headache, lymphadenopathy and rectal pain and bleeding.^{3,5,8-10}

There is no definitive treatment or specific antivirals for it; treatment usually involves management of symptoms and complications.^{3,8}

These complications may include pneumonitis, secondary bacterial infection and keratitis,⁴ with patients suffering from human immunodeficiency virus (HIV) being at a higher risk of complications and having more severe outcomes.¹¹ The aim of this study was to examine the incidence, demographics, clinical features, management, coexistence of other disease, clinical course and mortality in our region.

METHODOLOGY

Administrative and electronic medical records were used in this retrospective chart review. The Saudi Arabian Public Health Agency's definition of a confirmed case, which is consistent with CDC definition, was used. This study was conducted at King Khalid University Hospital, Riyadh, Saudi Arabia. The facility's emergency department receives around 100,000 adult visits per year.

Data were retrieved from the infection control department after gaining the approval of the Institutional Review Board office. The suspected case definition of Mpox was unexplained rash with fever, lymphadenopathy, back pain, headache or intense fatigue.⁶

After assessment, a sample is taken from the skin lesion of a patient suspected to have Mpox by a dermatologist. Both wet and dry swabs are taken from multiple lesions and sent to the public health laboratory, a national laboratory operated by the Saudi Arabian Ministry of Health. All suspected Mpox cases trigger a notification to the infection control department as testing is conducted in the national laboratory. Data on demographics, recent sexual contact and travel, clinical features, coexisting infections, treatments and outcome were recorded.

Statistical Analysis: We used SPSS version 27 (IBM Co., Armonk, NY, USA).

RESULTS

Data of 33 patients were retrieved to examine the occurrence of Mpox. After PCR testing, 16 positive Mpox cases were detected. The median age of patients with Mpox was 26.0 (IQR 10.0) years, and most of them were male and Saudis (93.8%, n=15). Six were single, five married and one was divorced. Only three recently traveled outside the country, and two others reported recent travels by their sexual partners (Table 1). Ten patients reported sexual contact within one patients engaged in sexual activity once, while seven had multiple instances of sexual contact (Table 2).

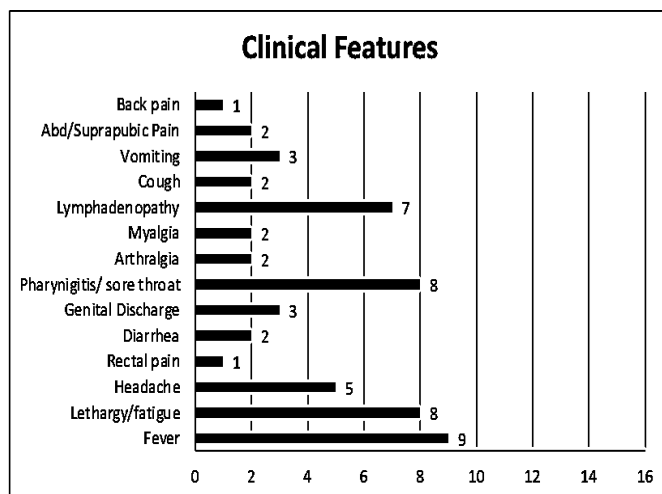


Fig. 1: Clinical features of Mpox in this study.

month preceding their presentation. Three
Table 1: History of patients' recent travel outside the country and that of their partners n=16).

Mpox cases (N=16)		
Recent travel outside the country	No	13
	Yes	3
Partner coming from travel	No	8
	Yes	2
	N/A	6
Mpox cases (N=3)		
Where did the patient come from	Bahrain	2
	Not documented	1
Mpox cases (N=2)		
Where did the partner come from	Zanzibar	1
	Not documented	1
Mpox cases (N=5)		
How long prior to presentation	2 weeks	1
	3 weeks	1
	1 month	1
	Not documented	2

All patients Mpox had a rash upon presentation, with a median duration prior to presentation of 4 days (IQR =2). Common site of rash was face and trunk (chest and abdomen), and genitals (Table 3). Pustules and papules were commonest type of rash (Table 4). Besides rash, fever, lethargy or fatigue and headache were common clinical (Fig. 1). Regarding coexisting sexually transmitted infections (STIs), none were found in all patients, as they tested negative for HIV, chlamydia, gonorrhea, syphilis, herpes simplex virus, hepatitis B and hepatitis C, even though some did not undergo the full diagnostic work-up.

Seven patients were administered antibiotics, one antiviral as a monotherapy, four both antivirals and antibiotics, and two received only symptomatic treatment. However, two patients received no treatment and were only isolated in the hospital. One patient suffered from blurry vision after experiencing skin eruption on the eyelid. The patient was seen by an

ophthalmologist and started on erythromycin drops empirically with no clear diagnosis.

DISCUSSION

With the recent outbreak, the higher prevalence of anogenital lesions in homosexual and bisexual men has heightened suspicions of sexual transmission of Mpox.^{5,12} In our cohort, only one patient reported recent homosexual contact, and six denied any recent sexual contact, which may suggest other modes of transmission or the plausible limitation of cultural or religious concerns that may reduce disclosure of such information. Documentation regarding these alternative transmission routes is generally inadequate.

Five patients reported protected intercourse, with one experiencing a condom breach, while the other five reported engaging in unprotected intercourse. This implies that relying solely on protective measures may not be sufficient in preventing transmission, as barrier methods do not eliminate skin-to-skin contact. Notably, only 31.25% had a travel-related history, raising concerns about potential underreporting and the likelihood of a higher actual case count in the region.^{13,14}

Cho⁸ evaluated clinical characteristics, incubation periods, typical symptoms, atypical symptoms, and reported a male preponderance exceeding 97%, with the proportion of those with homosexual and bisexual orientation surpassing 92%. We also had male predominance. This is similar to finding of a local study by Assiri et al.¹³ Disparities in reports of homosexual activities may stem from incomplete documentation, small sample size, religious considerations and societal stigma.

In a study from Qatar¹² among 12 patients, a predominant male sex distribution was observed, with 58.3% patients reporting exclusive heterosexual contact and 50% having recent travel history. In our study, 62.5% reported recent

Table 2: Sexual contact details.

Mpox cases (N=16)		
Sexual contact reports	No	6
	Yes	10
Mpox cases (N=10)		
Type of sexual contact	Heterosexual contact	9
	Homosexual contact	1
Type of contact (anal, vaginal, oral)	Anal	1
	Vaginal	4
	Vaginal & oral	1
	Not documented	4
	Unprotected - anal	1
Protected vs. Unprotected	Protected - vaginal	4
	Unprotected - vaginal	1
	Unprotected – not documented contact type	3
	Protected – not documented contact type	1
Long-time partner vs one-time	One-time	9
	Not documented	1
How many partners	One	5
	Multiple partners	5
How many times	Once	3
	Multiple times	7
Last contact prior to presentation	10 days prior	1
	12 days prior	1
	2 weeks prior	5
	1 month prior	3

sexual activity, contrary to the WHO report,¹⁵ which indicated that approximately 82.5% of cases were related to sexual contact.

Rash and skin lesions emerged as the most common clinical features in our study. Notably, 93.8% (n=15) had

Table 3: Rash locations.

Location	Number
Anogenital	15
Upper limbs	12
Face	12
Trunk (chest and abdomen)	11
Lower limbs	8
Back	6
Head and Neck	2

Table 4: Rash type and its details.

Type	Number
Pustules	15
Umbilicated pustules	8
Papules	6
Vesicles	2
Nodules	1
Ulcers	2
Plaques	1
With Crusting	10
With Erythematous base	11
Oral Mucosa Involvement	1
Pruritus	11
Pain	Painful 1
	Painless 15
Rash number	Mean (SD) 6.69 (2.12)

lesions predominantly in the anogenital region, followed by the trunk, face, and upper extremities. This pattern was also reported by Thornhill et al⁵ and Patel et al.¹⁰ However, Tarin-Vicente et al,⁹ reported the hands and feet as the most common areas. Unexpectedly, the occurrence of coexisting HIV infections, with rates ranging from 35.5% to 41% in other studies, was not observed in our study. This discrepancy may be attributed to our study's smaller sample size or the overall lower prevalence of HIV in the country.¹⁶ Similarly, tests for other STIs yielded negative results, albeit not conducted for all patients, underscoring a limitation of the study. No life-threatening complications developed in our cases. Contrarily, Thornhill et al⁵ and Patel et al,¹⁰ reported serious complications (including myocarditis, epiglottitis and severe penile edema), and Tarin-Vicente et al,⁹ found that proctitis was the most common complication. Zaqout et al,¹² reported severe proctitis and lower gastrointestinal

bleeding, miscarriage and paraphimosis. On the other hand, Assiri et al,¹³ did not report any complications, consistent with our finding.

The retrospective study design employed in this investigation poses a recognized limitation, restricting the scope to institutional cases and precluding an exhaustive examination of cases within the city or country. It is plausible that individuals with mild symptoms did not seek healthcare, introducing a potential source of bias. Moreover, a notable constraint comes from limitations in documentation, significantly impeding comprehensive data collection.

Furthermore, the absence of a standardized protocol for testing all STIs and variations in testing practices among managing physicians contribute to the limitation, as not all patients underwent comprehensive testing. To address these limitations, a nationwide initiative aimed at capturing all Mpox cases is strongly advocated. Efforts to standardize testing protocols for STIs would contribute to more comprehensive data collection.

CONCLUSION

The features of Mpox in the local context aligns with those documented in previous literature, albeit with potential variations in transmission patterns and occurrence of coexisting STIs. Emphasizing the significance of a high suspicion index, it is crucial to promptly undertake necessary measures such as testing and isolation.

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REFERENCES

1. Ladnyj ID, Ziegler P, Kima E. A human infection caused by monkeypox virus in Basankusu Territory, Democratic Republic of the Congo. *Bull World Health Organ* 1972;46:593-7.
2. Petersen E, Kantele A, Koopmans M, Asogun D, Yinka-Ogunleye A, Ihekweazu C, et al. Human monkeypox:

- epidemiologic and clinical characteristics, diagnosis, and prevention. *Infect Dis Clin North Am* 2019;33(4):1027-43.
3. Bunge EM, Hoet B, Chen L, Lienert F, Weidenthaler H, Baer LR, et al. The changing epidemiology of human monkeypox-A potential threat? A systematic review. *PLoS Negl Trop Dis* 2022;16:e0010141.
 4. World Health Organization. Mpox (monkeypox). [cited 2023 Nov 19]. Available from: <https://www.who.int/news-room/fact-sheets/detail/monkeypox>
 5. Thornhill JP, Barkati S, Walmsley S, Rockstroh J, Antinori A, Harrison LB, et al. Monkeypox Virus Infection in Humans across 16 Countries - April-June 2022. *N Engl J Med* 2022;387:679-91.
 6. Public Health Authority SM of H. Interim guidelines for monkeypox V1.4.2023. [cited 2023 Nov 19]. Available from: <https://covid19.cdc.gov.sa/wp-content/uploads/2023/06/Monkeypox-Guidelines-01-June-2023-V1.4.pdf>
 7. Centers for Disease and Control Prevention [homepage on the Internet]. Case definitions for use in the 2022 mpox response [Updated 2023 Nov 9; cited 2023 Nov 19]. Available from: <https://www.cdc.gov/poxvirus/mpox/clinicians/case-definition.html>
 8. Cho SY. The 2022 monkeypox outbreak in nonendemic countries: a review for the emergency department clinician. *Clin Exp Emerg Med* 2022;9:281-5.
 9. Tarín-Vicente EJ, Alemany A, Agud-Dios M, Ubals M, Suñer C, Antón A, et al. Clinical presentation and virological assessment of confirmed human monkeypox virus cases in Spain: a prospective observational cohort study. *Lancet* 2022;400:661-9.
 10. Patel A, Bilinska J, Tam JCH, Da Silva Fontoura D, Mason CY, Daunt A, et al. Clinical features and novel presentations of human monkeypox in a central London centre during the 2022 outbreak: descriptive case series. *BMJ* 2022;378:e072410.
 11. Ogoina D, Iroezindu M, James HI, Oladokun R, Yinka-Ogunleye A, Wakama P, et al. Clinical Course and Outcome of Human Monkeypox in Nigeria. *Clin Infect Dis* 2020;71:e210-4.
 12. Zaqout A, Daghfal J, Munir W, Abdelmajid A, Albayat SS, Abukhattab M, et al. Clinical manifestations and outcome of Mpox infection in Qatar: an observational study during the 2022 outbreak. *J Infect Public Health* 2023;16:1802-5.
 13. Assiri AM, Al-Tawfiq JA, Jokhdar HA, Algwezani AR, Albarraq AM, Alanazi KH, et al. Clinical features and outcome of human Mpox (Monkeypox) in Saudi Arabia: an observational study of travel-related cases. *J Infect Public Health* 2023;16:341-5.
 14. AlBahrani S, AlGarzai R, Aljunaid TO, Al-Tawfiq JA. A case report of mpox (monkeypox) in male traveler. *New Microbs New Infect* 2023;53:101132
 15. Multi-country outbreak of mpox, External situation report#29 – 20 October 2023 [Internet]. [cited 2024 Jan 10]. Available from: <https://www.who.int/publications/m/item/multi-country-outbreak-of-mpox--external-situation-report-29---20-october-2023>
 16. World Health Organization - Regional Office for the Eastern Mediterranean. [cited 2024 Jan 11]. Saudi Arabia HIV/AIDS country profile 2020. Available from: <https://www.emro.who.int/asd/country-activities/saudi-arabia.html>

Incidence of anti-tuberculosis drug induced liver injuries in patients receiving therapy at a tertiary care hospital in Karachi: A cross-sectional study

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Objective: To determine the prevalence and risk factors of anti-tuberculosis drug induced liver injury (AT-DILI) while assessing gender differences and documenting incidence trends.

Methodology: We utilized a questionnaire survey, collection of sputum samples for acid-fast bacilli testing and liver function tests (LFTs).

Results: Out 100 patients, 35 were males and 65 females. A total of 45 patients were tested positive for acid-fast bacilli (AFB) on smear. Most patients exhibited regular LFT results, signifying unremarkable

hepatic function during TB therapy. However, among relapse and post-TB cases, abnormal LFT findings were often accompanied by jaundice.

Conclusion: Among relapse and post-TB cases, abnormal LFT findings were often accompanied by jaundice. Further research is needed to elucidate mechanisms behind this increased vulnerability to prevent AT-DILI in populations.

Keywords: Anti-tuberculosis drug therapy, drug-induced liver injury, DILI, abnormal liver function, jaundice.

INTRODUCTION

Tuberculosis (TB) remains a significant global health concern, affecting millions of individuals worldwide.^{1,2} It is caused by *Mycobacterium tuberculosis*.³ The standard treatment involves a combination of anti-tuberculosis drugs,⁴ which has proven to be highly effective in combating the disease. But there is a risk in using these medications and one of those risks is damage to the liver. Officially called drug-induced liver injury (DILI), can look like mild elevations in the liver or go as far as causing severe hepatotoxicity, leading to liver failure.

Understanding how often this happens and its characteristics is important for several reasons.^{2,5} Firstly, it allows healthcare providers to assess the risk-benefit ratio of anti-tuberculosis drug therapy, particularly in patients with pre-existing liver conditions or other risk factors.² Secondly, it helps in the management of TB.⁶ The DOTS therapy has significantly reduced TB mortality rates and improved the prognosis.⁷ Studies,^{8,9} have reported the prevalence of AT-DILI among patients undergoing treatment at a tertiary care facility of our university-attached hospital located at Korangi. The aim of this study was to determine the prevalence and risk factors of AT-DILI while assessing gender differences and documenting incidence trends.

METHODOLOGY

This cross-sectional study was carried out at a tertiary

care hospital in Korangi, Karachi, from December 2022 and August 2023. The study was approved by IRB of Sohail University (Ref No. 000201/22 dated Aug 29, 2022). It utilized a questionnaire survey and involved the collection of sputum samples for acid-fast bacilli (AFB) testing and liver function tests (LFTs). The questionnaire covered background, medical history, medication usage, and any symptoms indicative of a potential liver injury. Consent was obtained from the 100 participating patients, who provided demographic information before discussing their medical history and current anti-tuberculosis drug regimen. Sputum samples were collected for AFB testing, ensuring the preservation of sample integrity, and subsequently sent to the lab for analysis. Additionally, liver function tests were conducted by obtaining samples for further laboratory analysis, focusing on measuring liver enzymes such as ALT, AST, and bilirubin levels. The recorded results, including questionnaire responses, AFB test outcomes, and LFT results, were entered into a secure database for subsequent analysis. Descriptive statistics summarized the demographic characteristics of the study population. The incidence of anti-tuberculosis drug-induced liver injuries was calculated based on the number of participants exhibiting abnormal LFT results.

Statistical Analysis: SPSS 25 was employed for data analysis, contributing to a comprehensive understanding of potential associations between medication use,

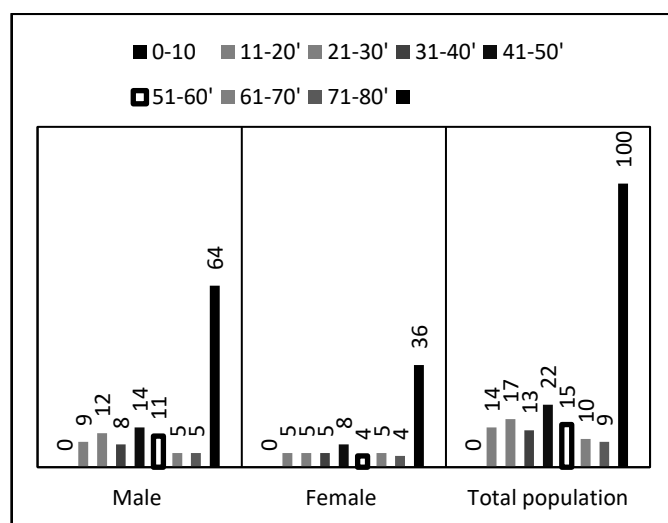


Fig. 1: Demographics of population.

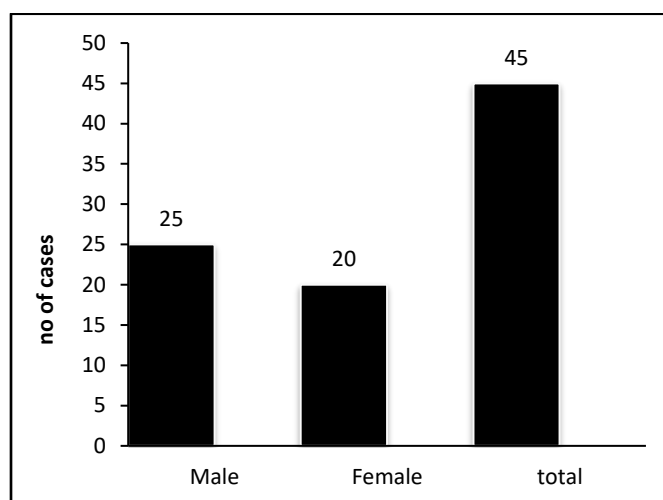


Fig. 2: Positive AFB by genders.

Table 1: Summaries of LFT and AFB and jaundice (n=100).

Parameter	Male	Female	AFB Positive	Normal LFT	Jaundice
Total Patients	35	65	7	-	-
AFB Positive Patients	5	2	7	-	-
Normal LFT	-	-	-	Majority	Relapse and post-TB
Abnormal LFT (Including Jaundice)	-	-	-	-	Relapse and post-TB

precisely anti-tuberculosis drugs, and liver injuries.

RESULTS

In a group of 100 patients, 35 were labeled males and the rest were females. However, when it came to AFB smear results, a total of seven people were infected with tuberculosis, 5 of them being males and in figure 1. Moving on to the assessment of Liver Function Tests (LFTs), most patients displayed average LFT results, suggesting normal liver function. Once their liver functions test was taken, it showed that there was a big issue within the subgroups that relapsed or had tuberculosis. Jaundice was the main concern here as it's a clear sign of liver injury. This finding raises a few questions about how much damage tuberculosis does to the liver and its treatment protocols. It also warrants further research in the care given to these specific patient groups the other 2 being females (Table 1 & 2).

DISCUSSION

Our study contributes valuable insights into AT-DILI

Table 2: General characteristics of TB and TB relapse cases on ATT.

		AFB-Positive	p- value
Total patients	100	45	0.001
Gender M: F	1:1	1:3	0.01
ATT- Therapy	First line (45)	Relapse (7)	
Abnormal LFT (Jaundice)	7	3	0.05

incidence, gender-specific patterns and the association with AFB positivity and previous knowledge on Isoniazid and rifampicin. These findings underscore the necessity for personalized monitoring strategies and highlight the importance of further research to elucidate the underlying mechanisms.⁸⁻¹¹ Integrating this knowledge into clinical practice will enhance the Safety and efficacy of tuberculosis treatment. Particularly in high-risk groups such as relapse patients and those with a history of tuberculosis, our present study aimed to investigate AT-DILI's incidence and risk factors among tuberculosis (TB) patients receiving therapy at a tertiary care hospital in Karachi. The study found an overall incidence of AT-DILI of 10.3%, with a slightly higher

risk for males (11.7%) than Females (8.3%). This finding is consistent with previous studies, which reported a male-to-female AT-DILI ratio ranging from 1.3:1 to 2.5:1.¹²

The study also found that AFB-positive TB patients were more susceptible to AT-DILI compared to AFB-negative patients (16.7% vs. 5.6%) on follow-up. This finding is said to be compatible with previous studies showing that AFB positivity is a significant risk factor for AT-DILI. The mechanism of AT-DILI is complex and needs to be fully understood. However, it is thought to involve multiple factors, including the direct toxic effects of ATT drugs, genetic.^{13,14} The most common ATT drugs associated with AT-DILI is isoniazid (INH) and rifampicin (RIF).¹⁴ INH is thought to cause liver injury through its metabolite, hydrazine, which can generate reactive oxygen species (ROS) and lead to lipid peroxidation.¹⁵ RIF is believed to cause liver injury through its induction of cytochrome P450 Enzymes can metabolize other drugs, including INH, into toxic metabolites.¹⁶

The incidence of AT-DILI in the present study (10.3%) is like that reported in other studies from Pakistan (7.7% to 13.6%).¹⁷ However, the incidence of AT-DILI in the present study is lower than that reported in studies from other countries, such as China (24.2%)¹⁸ and India (18.1%). All the first line ATT drugs are mostly metabolized by liver, thus involvement of cytochrome P450 enzymes, the drug-drug interactions (between isoniazid, rifampicin, and pyrazinamide).¹⁹ The overall incidence of AT-DILI in the present study (10.3%) is within the range of that reported in other studies (5% to 28%),¹⁴ suggests that AT-DILI is a relatively common complication of TB treatment.²⁰ The action of ATT drugs and the mechanism of liver injury are complex and beyond the scope of this discussion.²¹ However, a few key points can be made ATT drugs are effective in treating TB, but they can also cause side effects, including AT-DILI.²² The mechanism of AT-DILI is not fully understood, but it is thought it may involve multiple factors, including the direct toxic effects of ATT drugs, genetic predisposition, and immunological factors.^{23,24} The cross-sectional design precludes us from establishing causality or determining the temporal relationship between anti-tuberculosis drug use and liver injuries. Furthermore, the study's single site setting at a tertiary care hospital may limit the findings' applicability in other contexts. Longitudinal studies or randomized controlled trials (RCT) would be valuable in this regard. In addition, sample size may limit the study.

CONCLUSION

The results highlight the significance of routinely

checking liver function in patients taking anti-tuberculosis medication. Additional investigation is required to identify potential risk factors and create plans for the management and prevention of drug-induced liver injuries in this patient population. Our comprehensive study delves into the intricate landscape of anti-tuberculosis drug-induced liver injuries (AT-DILI) among patients receiving treatment at our esteemed tertiary care hospital.

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Drafting of the article: Saad Najam.
Critical revision of article for important intellectual content: Samia Pervaiz.
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REFERENCES

1. Raviglione M, Sulis G. Tuberculosis 2015: Burden, Challenges and Strategy for Control and Elimination. *Infect dis rep* 2016;8:6570.
2. Ramappa V, Aithal GP. Hepatotoxicity Related to Anti-tuberculosis Drugs: Mechanisms and Management. *J clin exp hepatol* 2013;3:37-49.
3. Bloom BR, Atun R, Cohen T, Dye C, Fraser H, Gomez GB, et al. Tuberculosis. In: Holmes KK, Bertozzi S, Bloom BR, Jha P, editors. *Major Infectious Diseases*. Washington (DC): The International Bank for Reconstruction and Development / The World Bank © 2017 International Bank for Reconstruction and Development / The World Bank.; 2017.
4. Medscape. Tuberculosis (TB) Treatment & Management.
5. Li X, Tang J, Mao Y. Incidence and risk factors of drug-induced liver injury. *Liver Int* 2022;42:1999-2014.
6. Li M, Luo Q, Tao Y, Sun X, Liu C. Pharmacotherapies for Drug-Induced Liver Injury: A Current Literature Review. *Front pharm* 2021;12:806249.
7. Alqahtani S, Kashkary A, Asiri A, Kamal H, Binongo J, Castro K, et al. Impact of mobile teams on tuberculosis treatment outcomes, Riyadh Region, Kingdom of Saudi Arabia, 2013-2015. *J epidemiol glob health* 2018;7:29-33.
8. Chen X, Hu TY. Strategies for advanced personalized tuberculosis diagnosis: Current technologies and clinical approaches. *Prec clin med* 2021;4:35-44.
9. Heyckendorf J, Georgiou SB, Frahm N, Heinrich N, Kontsevaya I, Reimann M, et al. Tuberculosis Treatment Monitoring and Outcome Measures: New Interest and New Strategies. *Clin microbiol rev* 2022;35:e002721.
10. Cohen KA, Manson AL, Desjardins CA, Abeel T, Earl AM. Deciphering drug resistance in Mycobacterium tuberculosis using whole-genome sequencing: progress,

- promise, and challenges. *Gen Med* 2019;11:45.
11. Tweed CD, Wills GH, Crook AM, Dawson R, Diacon AH, Louw CE, et al. Liver toxicity associated with tuberculosis chemotherapy in the REMoxTB study. *BMC medicine* 2018;16:46-9.
12. Kong X, Guo D, Liu S, Zhu Y, Yu C. Incidence, characteristics, and risk factors for drug-induced liver injury in hospitalized patients: A matched case-control study. *Br J Clin Pharmacol* 2021;87:4304-12.
13. Gaude GS, Chaudhury A, Hattiholi J. Drug-induced hepatitis and the risk factors for liver injury in pulmonary tuberculosis patients. *J fam med prim care* 2015;4:238-43.
14. Bao Y, Ma X, Rasmussen TP, Zhong XB. Genetic Variations Associated with Anti-Tuberculosis Drug-Induced Liver Injury. *Curr pharmacol rep* 2018;4:171-81.
15. Zhuang X, Li L, Liu T, Zhang R, Yang P, Wang X, et al. Mechanisms of isoniazid and rifampicin-induced liver injury and the effects of natural medicinal ingredients: A review. *Front pharmacol* 2022;13:1037814.
16. Kim JH, Nam WS, Kim SJ, Kwon OK, Seung EJ, Jo JJ, et al. Mechanism Investigation of Rifampicin-Induced Liver Injury Using Comparative Toxicoproteomics in Mice. *Int j mol sci* 2017;18.
17. Abid A, Subhani F, Kayani F, Awan S, Abid S. Drug induced liver injury is associated with high mortality-A study from a tertiary care hospital in Pakistan. *PloS one* 2020;15:e0231398.
18. Cavaco MJ, Alcobia C, Oliveiros B, Mesquita LA, Carvalho A, Matos F, et al. Clinical and Genetic Risk Factors for Drug-Induced Liver Injury Associated with Anti-Tuberculosis Treatment-A Study from Patients of Portuguese Health Centers. *J person med* 2022;12.
19. Devarbhavi H. Drug-Induced Liver Injury Unique to India. *Clin liver dis* 2021;18:108-10.
20. Moosa MS, Maartens G, Gunter H, Allie S, Chughlay MF, Setshedi M, et al. Rechallenge after anti-tuberculosis drug-induced liver injury in a high HIV prevalence cohort. *Southern Afr j HIV med* 2022;23:1376.
21. Clinton JW, Kiparizoska S, Aggarwal S, Woo S, Davis W, Lewis JH. Drug-Induced Liver Injury: Highlights and Controversies in the Recent Literature. *Drug safety* 2021;44:1125-49.
22. Molla Y, Wubetu M, Dessie B. Anti-Tuberculosis Drug Induced Hepatotoxicity and Associated Factors among Tuberculosis Patients at Selected Hospitals, Ethiopia. *Hepatic medicine. evid res* 2021;13:1-8.
23. Hosack T, Damry D, Biswas S. Drug-induced liver injury: a comprehensive review. *Therap Adv Gastroenterol* 2023;16:17562848231163410.
24. Saha A, Shanthi FXM, Winston AB, Das S, Kumar A, Michael JS, et al. Prevalence of Hepatotoxicity from Antituberculosis Therapy: A Five-Year Experience from South India. *J prim care commun health* 2016;7:171-4.

Evaluation of Patient safety skills among nursing students

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Objective: To evaluate the patient safety skills among nursing students in various academic settings.

Methodology: In this cross-sectional study, data were gathered from 320 university nursing students from September 2023 until February 2024 through Health Professional Education in Patient Safety Survey.

Results: There was a relation between patient safety awareness and GPA scores of the students ($p=0.024$). Clinical safety issues and understanding human & environmental factors were the highest safety domains

(3.92 ± 0.67), (3.91 ± 0.52). There was a statistically significant difference between the classroom and clinical setting in risk management domain ($p=0.033$).

Conclusion: For safe and effective patient care, nursing students should acquire the necessary competencies to navigate complex clinical environments and contribute to positive patient outcomes.

Keywords: Patient safety, nursing students, education.

INTRODUCTION

Patient safety is a fundamental aspect of healthcare delivery, and nurses play a crucial role in ensuring the well-being of patients. Nursing education programs are responsible for equipping students with the necessary skills to provide safe and quality care.¹ Evaluating the patient safety skills of nursing students is important to identify any gaps in their training and to make improvements where necessary.² Patient safety skills encompass a wide range of competencies, including but not limited to, medication administration, infection control, communication, critical thinking, and error prevention. Nursing students with a strong foundation in patient safety are better equipped to recognize potential risks and prevent adverse events in clinical settings.³

Traditional written examinations and multiple-choice tests are often augmented with objective structured clinical examinations and competency checklists to evaluate students' ability to apply patient safety principles in simulated and real-world scenarios.⁴ The use of standardized patient encounters allows for the assessment of communication skills and ethical decision-making related to patient safety.⁵ Interprofessional education and collaborative learning have shown promise in preparing nursing students to work effectively with other healthcare professionals to enhance patient safety.⁶

Exposure to patient safety principles during student clinical rotations has been associated with increased confidence and competence in identifying and addressing potential safety concerns in real patient care settings.⁷ Understanding and prioritizing patient safety skills can contribute to minimizing adverse events, reducing

medical errors, and ultimately improving patient outcomes.⁸ Nursing students must be cognizant of the legal and ethical responsibilities associated with patient safety. Understanding and practicing patient safety skills are crucial for adhering to regulatory requirements, maintaining professional standards, and upholding ethical obligations in patient care.⁹

Healthcare environments are complex, and patient safety is an ongoing concern. Nursing students who are well-versed in patient safety skills are better prepared to address the evolving challenges within healthcare systems, from technological advancements to emerging healthcare-associated infections and safety threats.¹⁰ Patient safety skills are often interwoven with effective communication, teamwork, and collaboration among healthcare professionals.¹¹ The aim of this study was to evaluate the patient safety skills among nursing students in our institution.

METHODOLOGY

This cross-sectional study was conducted from September 2023 until February 2024 and included 320 nursing students from faculty of nursing Prince Sattam bin Abdulaziz University. The study was approved by Prince Sattam bin Abdulaziz University's IRB (Ref No SCBR-188-2023) and an informed consent was completed by all participation.

Participants in the study were all undergraduate nursing students enrolled in the faculty of nursing, regardless of gender. The requirements for inclusion were completion of the "Fundamentals of Nursing Course," beginning clinical education, and not being hired by a hospital for

nursing students. The exclusion criterion was an incomplete questionnaire. Participants during clinical training sessions were given Health Professional Education in Patient Safety Survey. Of the 428 questionnaires we provided, 55 were returned unanswered and 43 were rejected because the instrument was not completed. Ultimately, an analysis of the data was conducted on 320 participants. To be included in the analysis, the overall response rate needed to be 74.48%.

Health Professional Education in Patient Safety Survey has 38 items in all, broken down into three categories. The first section's 27 elements, which cover seven dimensions (Table 1), are devoted to "learning about specific patient safety content areas." The factors and items are repeated for two different dimensions (clinical and classroom training) in accordance with the theoretical and practical nature of patient safety: participants were asked to respond separately. As a result, mean scores for the dimensions were determined for both clinical and educational settings.¹²

"How broader patient safety issues are addressed in health professional education" is the subject of the second half of the questionnaire, which consists of seven items. One of the four elements in the third section is "comfortable speaking up about patient safety." These sections rated on a 5-point scale that went from strongly disagree to strongly agree. Greater judgments of patient safety

Table 1: Measuring reliability of questionnaire.

Dimension	Items Number	Cronbach's Alpha Coefficient
Clinical safety issues	4-items	0.81
Team-working	6-items	0.79
Effective Communication	3-items	0.76
Risk management	3-items	0.82
Understanding human and environmental factors	3-items	0.71
Recognition, responsiveness to adverse events	4-items	0.73
Culture of safety	4-items	0.79
What a broader patient safety issues are addressed in health professional education	7-items	0.84
Comfortable speaking up about patient safety	4-items	0.78

Table 2: Participant's personal characteristics and their relation to patient safety awareness (n=320).

Personal Characteristics	Total	%	Mean±SD	χ^2 /(p)
Age				
• Less than 21 years	98	30.6	3.28±0.54	2.075/ (0.091)
• 21-<24 years	158	49.4	3.31±0.82	
• 24 years and more	64	20.0	3.65±0.75	
GPA score				
• Low (less than 2)	91	28.4	3.21±0.62	5.098/ (0.024*)
• Medium (2-3.5)	154	48.2	3.54±0.64	
• High (more than 3.5)	75	23.4	3.91±0.45	
What is your gender?				
• Male	122	38.1	3.72±0.65	1.019/ (0.149)
• Female	198	61.9	3.85±0.59	
Attending patient safety training				
• Yes	21	6.6	3.80±0.71	2.107/ (0.112)
• No	299	93.4	3.45±0.54	
Observing medical or nursing errors				
• Yes	48	15.0	3.79±0.75	1.429/ (0.127)
• No	272	85.0	3.43±0.60	
Reporting errors to educator or hospital staff				
• Yes	35	10.9	3.71±0.65	0.897/ (0.478)
• No	285	89.1	3.65±0.72	

χ^2 =chi-square test.

*Significant ($p<0.05$).

Table 3: Assessment of patient safety domains among in classroom and clinical field.

Variable	Class	Clinical	t	p
Clinical safety issues	3.92±0.67	3.78±0.72	2.093	0.173
Team-working	3.87±0.55	3.88±0.65	0.931	0.681
Effective Communication	3.74±0.89	3.81±0.92	3.003	0.109
Risk management	3.89±0.75	3.28±0.77	6.137	0.033*
Understanding human and environmental factors	3.77±0.54	3.91±0.52	1.136	0.237
Recognition, responsiveness to adverse events	3.22±0.82	3.48±0.47	1.016	0.372
Culture of safety	3.46±0.73	3.57±0.72	3.129	0.098
Total	3.82±0.64	3.79±0.56	3.435	0.095

t=paired t-test.

*Significant (p<0.05).

Table 4: Perception and comfort speaking up about patient safety among students.

Broader aspects of patient safety	Mean ± SD	Agreement	Disagreement
My scope of practice was very clear.	3.59±0.98	205(64.1)	115(35.9)
There is consistency in how patient safety issue were dealt.	3.67±0.87	239(74.7)	81(25.3)
I had sufficient opportunity to learn and interact with members of interdisciplinary teams.	3.73±0.91	248(77.5)	72(22.5)
I gained a solid understanding that reporting adverse events and close calls can lead to change and reduce reoccurrence of events.	3.42±0.64	198(61.9)	122(38.1)
Patient safety was well integrated into program.	3.63±0.77	231(72.2)	89(27.8)
Clinical aspects of patient safety were well covered in program.	3.48±0.82	201(62.8)	119(37.2)
System of patient safety were well covered in program.	3.82±0.82	251(78.4)	69(21.6)
Total	3.69±0.79	225(70.3)	95(29.7)
Comfort speaking up about patient safety			
If I see someone engaging in unsafe care practice, I feel I can approach them.	3.62±0.58	222(69.4)	98(30.6)
If I make a serious error, I worry that I face disciplinary action.	3.54±0.64	213(66.6)	107(33.4)
It is difficult to question the actions of those with more authority.	3.72±0.83	229(71.6)	91(28.4)
In clinical\simulation settings discussion around adverse events focuses mainly on system-related issues, rather than focusing on the individual.	3.83±0.71	247(77.2)	73(22.8)
Total	3.71±0.80	228(71.2)	92(28.8)

expertise, broader perspectives on patient safety, and comfort speaking up about patient safety are all indicated by higher ratings.

Seven Port-Said University faculty members who specialize in nursing administration gave their approval

for the questionnaire's content validity. Twenty-five seventh- and eighth-level nursing students who were not involved in the study were requested to complete the questionnaire to evaluate its reliability. The Cronbach's alpha coefficient was utilized to evaluate the

dependability of every segment.

Statistical Analysis: Chi-square test was used to assess the relation between personal characteristics and patient safety awareness among study participants. Paired sample t-test was used to compare means of classroom and clinical setting safety domains. Cronbach alpha test (α) was used to measure the reliability of the study variables. Data analysis was performed using IBM SPSS statistics 23 with the significance level at $p < 0.05$.

RESULTS

Table 2 shows that approximately half of student's age ranged from 21 to less than 24 years, also around half of the students have GPA scores from 2:3.5, 61.9% of the students were female; 93.4 of them not attending any training regarding patient safety. Finally, there is a relation between patient safety awareness and GPA scores of the students ($p = 0.024$).

Table 3 presents that clinical safety issue was the higher domain in classroom safety (3.92 ± 0.67), while understanding human and environmental factor was the higher domain among clinical safety domains (3.91 ± 0.52), also there is a statistically significant difference between the classroom and clinical setting in risk management domain ($p\text{-value} = 0.033$). Table 4 illustrates that the system of patient safety was well covered in our program was the higher agreement item among the broader aspects of patient safety (78.4%). Moreover, discussion around adverse events focuses mainly on system-related issues, rather than focusing on the individual was the highest item among Comfort speaking up about patient safety (77.2%).

DISCUSSION

Various studies have highlighted the need for nursing students to develop competencies in areas such as communication, teamwork, critical thinking, and problem-solving to effectively navigate the complex healthcare environment with a focus on patient safety.¹³ This study found a relation between patient safety awareness and GPA scores of the students, this finding means that students with high GPA scores have also high mean scores in patient safety awareness. Nursing students who excel in patient safety skills often demonstrate a mindset focused on quality improvement and patient advocacy. This mindset contributes to improved student outcomes by reinforcing a commitment to ongoing learning, reflective practice, and a dedication to continuous enhancement of patient care practices.¹⁴

In the same line, a study found a connection between the higher achievement of the nursing students and their perception regarding patient safety issues, nursing

students with advanced patient safety skills demonstrate increased clinical competence, as they are better equipped to recognize and address potential risks to patient safety.¹⁵ Disagreed with this finding, another study found that age of student plays an important role in shaping the perception of patient safety, senior nursing students have higher awareness of patient safety.¹⁶

Additionally, clinical placements play a crucial role in exposing nursing students to real-world healthcare settings and helping them apply their theoretical knowledge to practice. During these placements, students can observe experienced nurses, participate in patient care activities, and learn about the importance of teamwork, effective communication, and error prevention in ensuring patient safety.¹⁷ Nursing students with strong patient safety skills are better prepared to engage in effective communication with colleagues, patients, and interdisciplinary teams, fostering positive collaboration and teamwork in clinical settings.¹⁸

Consistent with those findings, higher patient safety skills are associated with improved professional readiness among nursing students. This preparation encompasses their ability to integrate safety protocols, manage complex patient care scenarios, and apply evidence-based practices, ultimately leading to increased confidence and preparedness for real-world practice.¹⁹ As nursing students engage with patient safety concepts, they refine their skills in assessing, analyzing, and addressing potential safety concerns, which enhances their overall clinical decision-making capabilities.²⁰

Nursing students with advanced patient safety skills demonstrate improved awareness and understanding of ethical dilemmas, professional standards, and legal responsibilities, all of which contribute to higher ethical decision-making and adherence to best practices.²¹ Studying patient safety skills among nursing students is crucial for ensuring that future nurses are equipped to deliver safe, high-quality care, contribute to a culture of safety, and navigate the complexities of the healthcare system while upholding legal and ethical standards. It is an essential component of nursing education, with far-reaching implications for patient well-being and the broader healthcare landscape.²²

CONCLUSION

Evaluating the patient safety skills of nursing students is crucial to ensure the delivery of high-quality care in healthcare settings, this can bridge any gaps in nursing education programs and enhance the training of future nurses in patient safety practices.

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REFERENCES

- Hyatt RD. Nurse Perceptions: The Relationship Between Patient Safety Culture, Error Reporting and Patient Safety in US Hospitals (Doctoral dissertation, Franklin University).
- Ghasempour M, Ghahramanian A, Zamanzadeh V, Valizadeh L, Onyeka TC, Jafarabadi MA. Senior nursing student's confidence in learnt competencies and perceptions of patient safety competency: a multisite cross-sectional study. *BMJ Open* 2023;13:e070372.
- Hayat AA, Keshavarzi MH, Zare S, Bazrafcan L, Rezaee R, Faghihi SA, et al. Challenges and opportunities from the COVID-19 pandemic in medical education: a qualitative study. *BMC Med Educ* 2021;21:247-9.
- Vosoughi MN, Zamanzadeh V, Valizadeh L, Ghahramanian A, Lotfi M, Bagheriyeh F, et al. An introduction to the TPSN model: a comprehensive approach to reducing the theory-practice gap in nursing. *BMC Nursing* 2022;21:261-4.
- Lee SE, Morse BL, Kim NW. Patient safety educational interventions: A systematic review with recommendations for nurse educators. *Nursing Open* 2022;9:1967-79.
- Basson T, Montoya A, Neily J, Harmon L, Watts BV. Improving patient safety culture: a report of a multifaceted intervention. *J Pat Safety* 2021;17:e1097-104.
- Bartoničková D, Kohanová D, Mazalová L, Brišová K, Bomberová M, Žiaková K. Nursing students' assessment of patient safety competencies: a pilot study. *Cent Eur J Med* 2024;15:1050-8.
- Tarhan M, Elibol E. The effect of a brief mindfulness-based stress reduction program on strengthening awareness of medical errors and risks among nursing students. *Nur Educ Pract* 2023;70:103655.
- Jafari MJ, Mostafazadeh P, Mojebi MR, Nemati-Vakilabad R, Mirzaei A. Identifying predictors of patient safety competency based on sleep quality in student faculty of nursing and midwifery during the internship period: a multidisciplinary study. *BMC Nursing* 2024;23:67-72.
- De Miguel MS, de Elguea JO, Gómez-Gastiasoro A, Urcola F, Cid-Expósito MG, Torres-Enamorado D, et al. Patient safety and its relationship with specific self-efficacy, competence, and resilience among nursing students: a quantitative study. *Nur Educ Today* 2023;121:105701.
- Farokhzadian J, Eskici GT, Molavi-Taleghani Y, Tavan A, Farahmandnia H. Nursing students' patient safety competencies in the classroom and clinical settings: a cross-sectional study. *BMC Nursing* 2024;23:47-51.
- Ginsburg L, Castel E, Tregunno D, Norton PG. The H-PEPSS: an instrument to measure health professionals' perceptions of patient safety competence at entry into practice. *BMJ Qual Safety* 2012;21:676-84.
- Lee SE, Dahinten VS. Evaluating a patient safety course for undergraduate nursing students: A quasi-experimental study. *Collegian* 2023;30:75-83.
- Alidousti-Shahraki N, Farzi S, Tarrahi MJ. Psychometric properties of the Persian version of the health professionals education in patient safety survey. *Nurs Midwif Stud* 2022;11:51-61.
- Song MO, Yun SY, Jang A. Patient Safety Error Reporting Education for Undergraduate Nursing Students: A Scoping Review. *J Nurs Educ* 2023;62:489-94.
- Elsehrawy M, Gaber H, Adam S. Nurse's awareness regarding patient safety culture at Mansoura University Hospital. *Mans Nurs J* 2015;2:137-46.
- Boloré S, Sovet L, Guirimand N. Health professionals' perceptions of patient safety competencies: psychometric properties of the French version of the H-PEPSS in France and Switzerland. *BMC Med Educ* 2023;23:905-9.
- Song MO, Kim S. The experience of patient safety error for nursing students in COVID-19: focusing on King's conceptual system theory. *Int J Environ Res Public Health* 2023;20:2741.
- Ramírez-Torres CA, Rivera-Sanz F, Cobos-Rincon A, Sufrate-Sorzano T, Juárez-Vela R, Gea-Caballero V, et al. Perception of patient safety culture among nursing students: A cross-sectional study. *Nurs Open* 2023;10:7596-602.
- Alsulami A, A'aqoulah A, Almutairi N. Patient safety culture awareness among healthcare providers in a tertiary hospital in Riyadh, Saudi Arabia. *Front Public Health* 2022;10:953393.
- Park O, Jeon M, Kim M, Kim B, Jeong H. The Effects of a Simulation-Based Patient Safety Education Program on Compliance with Patient Safety, Perception of Patient Safety Culture, and Educational Satisfaction of Operating Room Nurses. In *Healthcare* 2023;11:2824.
- Mortensen M, Naustdal KI, Uibu E, Mägi L, Kangasniemi M, Pölluste K, et al. Instruments for measuring patient safety competencies in nursing: a scoping review. *BMJ Open Qual* 2022;11:e001751.

Exploring the effect of different treatment modalities on health outcome in osteoporosis; A follow-up study

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Objective: To determine the effect of different treatment modalities on health outcomes in patients with osteoporosis.

Methodology: The study was conducted at a Medicare Cardiac and General Hospital and used a longitudinal design to follow up on participants from the Orthopedic Outpatient Department who were aged 35-60 or older and diagnosed with osteoporosis based on their DEXA scan T score. At the baseline, demographic data, medical history, physical activity, joint discomfort, periodontal pocket, and clinical attachment level were recorded. Intravenous bisphosphonate of 3 mg every 3 months, subcutaneous denosumab of 60mg every 6 months, along with calcium supplements (1200 mg/day) and vitamin D (600 IU/day) were administered. After a 1-year follow-up, the outcome variables were measured and compared to the baseline. The statistical analysis was performed using SPSS software and paired T-tests, and the Fischer exact test were used.

Results: The study included 200 participants, with mean age of 61.36±10.42 years and a mean BMI of 31.58±16.52. After 12 months of therapy, significant differences were observed in physical health outcomes, with the bisphosphonate group showing superior results in joint discomfort and physical activity compared to the denosumab group (p<0.001). Moreover, the bisphosphonate group demonstrated significantly higher clinical attachment level and shallower periodontal pocket depth, suggesting potential improvement in periodontal health (p<0.001).

Conclusion: Bisphosphonate treatment may be more effective than denosumab in reducing joint pain, overall health, and periodontal health in individuals with osteoporosis, underscoring the importance of personalized treatment strategies in clinical practice.

Keywords: DEXA, osteoporosis. bisphosphonate, denosumab, physical & periodontal health.

INTRODUCTION

Osteoporosis is a chronic skeletal disease characterized by a decrease in bone quantity and quality, increasing fracture risk, and causing bone fragility.¹ In Asia, where 200 million women are afflicted, the significance of prompt treatment is emphasized.² The WHO defines osteoporosis using BMD measurements of the spine, hip, or forearm. Normal BMD T-scores are within 1 SD; low bone mass or osteopenia is -1 to -2.4 SD; and osteoporosis is -2.5 standard deviations or more.³ DEXA scan of the hip and spine is the preferred method for diagnosis of osteoporosis.⁴

Osteoporosis is linked to a higher incidence of low-energy fractures affecting the vertebral column, hip, distal humerus, and forearm.⁵ Risk factors include low BMD, age, fragility fracture history, and familial history of osteoporosis. Other factors, like gender, calcium intake, physical activity, menopausal age, and vitamin D deficiency, also impact BMD. Genetics significantly influences bone microarchitecture and BMD.⁶ Postmenopausal osteoporosis is treated with approved medications including teriparatide, bisphosphonate, denosumab, and selective estrogen receptor modulators.

Bisphosphonates (BPs) prevent bone resorption and inhibit osteoclastic activity. They decrease bone turnover, increase bone density, and reduce fracture risk.⁷ Nitrogen-containing BPs (N-BPs) and simpler BPs (etidronic acid and clodronate) have distinct molecular mechanisms of action. N-BPs, like pamidronate, alendronate, risedronate, ibandronate, risedronate, and zoledronate, inhibit enzymes in the mevalonate/cholesterol biosynthesis pathway.⁸

Denosumab, a humanized monoclonal antibody, neutralizes RANKL, a cytokine that affects the recruitment, maturation, and survival of osteoclasts by binding to the RANK receptor on their outer membrane.⁹ Teriparatide is a pure anabolic medication, that promotes bone growth and reduces fracture incidence in postmenopausal women.¹⁰

Periodontitis is a chronic inflammatory disease that slowly affects the teeth and results in the degradation of the periodontal ligament, cementum, gingiva, and alveolar bone.¹¹ This condition is predisposed by multiple factors, such as bacterial plaque, genetic predisposition, obesity, and a diet high in inflammatory compounds.¹² Osteoporosis and periodontitis are two distinct diseases

that lead to changes in bone metabolism and are associated with age and inflammation.¹³ The host's response to periodontal disease can potentially influence osteoporosis development and vice versa due to the intricate nature of host reactions.¹⁴ Osteoporosis can disrupt the resorption of alveolar bone due to an inflammatory process resulting from an imbalance between the host's immune system and dental plaque.^{15,16}

It is recommended that individuals with bone fragility, post-menopausal patients, and those with other medical conditions undergo periodontal exams, regardless of whether therapy for antimetabolic diseases is required.¹⁷ The aim of this study was to determine the effect of different treatment modalities on health outcomes in patients with osteoporosis.

METHODOLOGY

The study used a longitudinal (follow-up) design to assess the effects of antiresorptive (AR) drugs on physical activity, joint pain, periodontal pocket, and clinical attachment level (CAL). The study was conducted at the Medicare Cardiac and General Hospital Orthopedic Outdoor Patient Department, from September 2022 to September 2023. Ethical approval was obtained from the IRB (Protocol: 000203/22) at Sohail University, Karachi, Pakistan and an Informed written consent was obtained from all participants.

The study included 200 participants aged 35 to 60 years or older, both gender, who had complained of joint pain, those who had been diagnosed with osteoporosis and BMD scores below $-2.0 \pm \text{SD}$, and those who provided informed consent for participation. We excluded individuals with severe comorbidities or those who cannot follow the procedure due to the potential impact on results. The WHO Sample Size Calculator was used for the calculation of the sample size, referencing a South Asian population.¹⁸ The sample size came to be 170, calculated using the population mean of t-scores by DEXA scan with a 5% significance level and 90% power of the test.

We used individual matching techniques and administered intravenous bisphosphonate of 3 mg every 3 months, subcutaneous denosumab of 60mg every 6 months, along with calcium supplements (1200 mg/day) and vitamin D (600 IU/day). The variables used for propensity score matching included age, BMI, occupation, monthly income, physical activity, and DEXA

Table 1: Socio-demographic characteristics of study participants (N=200).

Variable		Frequency	%
Age	35 - 50 year	23	11.5%
	51-65 year	112	56%
	>65 year	65	32.5%
Gender	Male	14	7%
	Female	186	93%
Education Status	Uneducated	13	6.5%
	Secondary	36	18%
	Intermediate	112	56%
	Bachelor & Higher	39	19.5%
Occupation	Unemployed	12	6%
	Own Business	3	1.5%
	Housewife	152	76%
	Job in Organization	33	16.5%
Body Mass Index	19-30	104	52%
	31-40	89	44.5%
	Above 40	7	3.5%
Fracture Risk	Decreased	15	7.5%
	Normal	92	46%
	Increased	93	46.5%
Antiresorptive drugs	Bisphosphonate	132	66%
	Denosumab	68	34%

scan T scores at baseline. Physical and periodontal health were assessed before the start of AR therapy. After 12 months of therapy, patients were examined for their related outcomes.

Study variables include age and BMI. Physical activity 0 unable to walk, 0.5 less than 30 minutes per day, and 1 greater than 30 minutes before the treatment at baseline and after the treatment 0 unable to walk, 0.5 as 30 minutes per day, and 1 as 60 minutes, 1.5 consider as 90 minutes, 120 minutes consider as 2, 150 minutes consider as 2.5, 180 minutes as 3. A periodontal probe was used to measure the periodontal pocket and CAL.

Statistical Analysis: Data were analyzed through SPSS version 22. For inferential statistics, Paired T-tests were used to determine pre- and post-treatment changes in physical activity, CAL, and periodontal pocket depth before and after antiresorptive medication. Secondary

Table 2: Physical and periodontal outcomes.

Outcomes Variable	Bisphosphonate			Denosumab		
	Mean±SD	p-value	CI	Mean±SD	p-value	CI
Physical Activity						
Pre-Treatment	.59±.333	<0.01*	-1.58 - -1.44	.41±.310	<0.01*	0.55 -0.47
Post-Treatment	2.10±.67			.92±.348		
Pocket Depth						
Pre-Treatment	5.85 ±.682	<0.01*	1.18 - 1.34	5.91±.663	<0.01*	0.11 -0.32
Post-Treatment	4.58 ± .631			5.69± .797		
Clinical Attachment Level (CAL)						
Pre-Treatment	5.34 ±.640	<0.01*	0.50- 0 .71	5.24 ±.715	<0.01*	0.11 - 0.33
Post-Treatment	4.73±.828			5.01 ± .763		
Joint Pain Pre Treatment	Frequency	%	p-value	Frequency	%	p-value
Yes	132	100%	<0.01 [†]	68	100%	<0.01 [†]
No						
Joint Pain Post-Treatment						
Yes	9	6.8%		39	57.4%	
No	123	93.2%		29	42.6%	

[†]P-value measured By McNemar *P-value by Paired T-Test (<0.05 considered significant)

outcome joint pain was measured before and after the medication using the McNemar test. Paired T-tests were used to assess differences between before and after the treatment in the same group of people. $p < 0.05$ was considered significant.

RESULTS

The demographic characteristics of participants are presented in Table I, which shows that their mean age was 61.36 ± 10.42 years and their mean BMI was 31.58 ± 16.52 . After 12 months of AR treatment, results in Table 2 showed significant improvements in these variables, with $p < 0.01$, indicating the effectiveness of these medications in increasing physical activity, reducing joint discomfort, and improving periodontal health.

DISCUSSION

This study had 200 cases with an average age of 61.36 ± 10.42 years. Notably, 56% were aged between 51 and 65 years and 93% were female. These findings are similar to those reported by Abirami et al.¹⁹ A study found that a higher proportion of male participants were highly educated (87.2%) and employed (100.0%).²⁰ Furthermore, obesity, personal, and family history of osteoporosis were more prevalent among females, with

rates of 38.8%, 16.9%, and 25.6%, respectively, compared to males.²⁰

Akhlaque et al, reported 42.2% were male, with an average age of 65 ± 10 years.²¹ The higher proportion of females affected by osteoporosis may be due to factors such as hormonal differences, longer life expectancy, and lower peak bone mass compared to males, as well as lifestyle factors like lower physical activity levels and higher prevalence of low calcium intake among females. In this study, 52% participants had a BMI between 19 and 30, (average 31.58 ± 16.52 kg/m²). Ibrahim et al, had approximately 85% of patients with BMI up to 29.9 kg/m.²⁰ In this study, after 12 months of AR treatment, the average score of physical activity significantly increased, and pocket depth significantly decreased, accompanied by a decrease in pain up to 93.2% among patients treated with bisphosphonates compared to baseline measurements ($p < 0.001$).

However, denosumab treatment also showed significant improvement compared to baseline measurements ($p < 0.05$), albeit to a lesser extent than bisphosphonate treatment. Narayanasamy et al, reported that the intravenous treatment was simpler to comprehend, more efficient, less demanding with fewer associated costs, and a preferred regimen when compared to oral BPs.²² Atta

et al, reported that BP therapy had a positive effect on fracture rate, BMD, mobility score, well-being and pain episodes as in their study mobility score was 0.94 ± 1.30 at baseline and 2.5 ± 1.02 at the end of the treatment ($p < 0.001$), followed by pain episode improved from 24.1 ± 8.15 to 2.7 ± 8.31 ($p < 0.001$).²³

A review-based study by Tzschentke et al, concluded that there was a growing body of evidence supporting effectiveness of BPs in chronic pain conditions, reduced bone turnover, and an increase in BMI, although the availability of well-designed studies remains somewhat limited.²⁴

This study has several limitations, including a small sample size, a single-center study, and a lack of analysis regarding safety measures. Each drug group should have equal participation. The study duration was short. Large-scale multicenter longitudinal studies are recommended to further validate these findings.

CONCLUSION

The use of bisphosphonate and denosumab has shown promising results in reducing joint pain, increasing physical activity, and improving periodontal health.

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REFERENCES

- Nuti R, Brandi ML, Checchia G, Di Munno O, Dominguez L, Falaschi P, et al. Guidelines for the management of osteoporosis and fragility fractures. *Intern Emerg Med* 2019;14:85–102.
- Epidemiology-of-Osteoporosis-and-Fragility-Fractures @ Www.Osteoporosis.Foundation [Internet]. Available from: <https://www.osteoporosis.foundation/facts-statistics/epidemiology-of-osteoporosis-and-fragility-fractures>
- Sozen T, Ozisik L, Calik Basaran N. An overview and management of osteoporosis. *Eur J Rheumatol* 2017;4:46–56.
- International Atomic Energy Agency. Dual energy X ray absorptiometry for bone mineral density and body composition assessment - Hum Health Series 2010;1–132.
- Johnell O, Kanis JA. An estimate of the worldwide prevalence and disability associated with osteoporotic fractures. *Osteoporos Int* 2006;17:1726–33.
- Tarantino U, Iolascon G, Cianferotti L, Masi L, Marcucci G, Giusti F, et al. Clinical guidelines for the prevention and treatment of osteoporosis: summary statements and recommendations from the Italian Society for Orthopaedics and Traumatology. *J Orthop Traumatol* 2017;18:3–36.
- Center JR, Lyles KW, Bliuc D. Bisphosphonates and lifespan. *Bone* 2020;141:115566.
- Ebetino FH, Sun S, Cherian P, Roshandel S, Neighbors JD, Hu E, et al. Bisphosphonates: The role of chemistry in understanding their biological actions and structure-activity relationships, and new directions for their therapeutic use. *Bone* 2022;156:116289.
- Kendler DL, Cosman F, Stad RK, Ferrari S. Denosumab in the Treatment of Osteoporosis: 10 Years Later: A Narrative Review. *Adv Ther* 2022;39:58–74.
- Zhang D, Potty A, Vyas P, Lane J. The Role of Recombinant PTH in Human Fracture Healing. *J Orthop Trauma* 2014;28:57–62.
- Petersen PE, Baehni PC. Periodontal health and global public health. *Periodontol* 2012;60:7–14.
- Chapple ILC, Bouchard P, Cagetti MG, Campus G, Carra M, Cocco F, et al. Interaction of lifestyle, behaviour or systemic diseases with dental caries and periodontal diseases: consensus report of group 2 of the joint workshop on the boundaries between caries and periodontal diseases. *J Clin Periodontol* 2017;44:39–51.
- Yu B, Wang C. Osteoporosis and periodontal diseases – An update on their association and mechanistic links. *Periodontology* 2022;89:99–113.
- Loos BG, Van Dyke TE. The role of inflammation and genetics in periodontal disease. *Periodontology* 2020;83:26–39.
- Nibali L, D'Aiuto F, Griffiths G, Patel K, Suvan J, Tonetti MS. Severe periodontitis is associated with systemic inflammation and a dysmetabolic status: a case-control study. *J Clin Periodontol* 2007;34:931–7.
- Xu S, Zhang G, Guo J, Tan Y. Associations between osteoporosis and risk of periodontitis: A pooled analysis of observational studies. *Oral Dis* 2021;27:357–69.
- Sanz M, Herrera D, Kebschull M, Chapple I, Jepsen S, Berglundh T, et al. Treatment of stage I–III periodontitis—The EFP S3 level clinical practice guideline. *J Clin Periodontol* 2020;47:4–60.
- Kotwal N, Upreti V, Nachankar A, Hari Kumar KS. A prospective, observational study of osteoporosis in men. *Indian J Endocrinol Metab* 2018;22:62–6.
- Abirami P, Nithya M, Priyanka K, Hemalatha G. Assess the Prevalence of Osteoporosis Among Middle Aged Women in Mamandur. *Int J Pharm Clin Res* 2017;9:690–5.
- Ibrahim HA, Nahari MH, Al-khadher MA, Ismail NI, Elgzar WT. Gender Disparities in Osteoporosis Knowledge, Health Beliefs and Preventive Behaviors in Najran City, Saudi Arabia. *Nutrients* 2023;15:1–13.

21. Akhlaque U, Ayaz S Bin, Akhtar N, Ahmad N. Association of bone mineral density and body mass index in a cohort of Pakistanis: Relation to gender, menopause and ethnicity. *Egypt Rheumatol* 2017;39:39–43.
22. Narayanasamy M, Bishop S, Sahota O, Paskins Z, Gittoes N, Langley T. Acceptability, and engagement amongst patients on oral and intravenous bisphosphonates for the treatment of osteoporosis in older adults. *Age Ageing* 2022;51:1-11.
23. Atta I, Iqbal F, Lone SW, Ibrahim M, Khan YN, Raza J. Effect of intravenous pamidronate treatment in children with osteogenesis imperfecta. *J Coll Physicians Surg Pak* 2014;24:653–7.
24. Tzschentke TM. Pharmacology of bisphosphonates in pain. *Br J Pharmacol* 2021;178:1973–94.

Frequency of anxiety and depression among patients undergoing renal dialysis

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Objective: To identify the frequency of anxiety and depression among patients undergoing renal dialysis.

Methodology: This descriptive cross-sectional study was conducted at the Nephrology department of Chandka Medical College, Larkana from August to December 2022. Diagnosed cases of chronic kidney disease undergoing renal dialysis were enrolled. Depression and anxiety were assessed as per the Hospital Anxiety and Depression Scale (HADS). Depression and anxiety were categorized as normal, borderline, and abnormal as per HADS. The data were analyzed by SPSS 22.

Results: Out of 175 participants with an average age of 54.26±15.42 years, 65.1% were males and 34.9% females. Duration of dialysis in 100 (57.10%) patients

was more than one year, 48 (27.40%) had the duration for less than one year, and 27 (15.40%) had a duration of less than one month. Amongst all, 117 (66.90%) had anxiety disorder, 37 (21.10%) were borderline for anxiety disorder, and 21 (12.0%) were not having anxiety disorder. Depression was as follows: 92 (52.60%) were abnormal, 48 (27.40%) had borderline depression, and 35 (20.0%) were not having depression. Anxiety and depression were statistically significant, with the duration of renal dialysis having a p value of 0.019 and 0.001, respectively.

Conclusion: Anxiety and depression among patients with chronic kidney disease undergoing hemodialysis are quite high and alarming.

Keywords: Anxiety, depression, dialysis.

INTRODUCTION

The lives of those who have end-stage renal disease (ESRD) are significantly impacted. Patients' lives are profoundly impacted by the experience of many losses, including renal function, family role, work role, sexual function, time, and mobility.¹ Dialysis patients with ESRD go through significant changes and adaptations in their social, professional, and personal lives.¹ Once on dialysis, the patient's mental health and quality of life are affected by stresses such as time and dietary restrictions, illness-related unemployment, changes in sexual desire and behavior, increased financial load, and dread of death.²

The most prevalent psychopathological disorder among ESRD patients is depression.³ Several factors seem to trigger anxiety and depression in hemodialysis patients such as co-morbidities, frequent hospitalizations,⁴ chronic pain, sleep disturbances,⁵ chronic inflammation, increased fatigue, decreased sexual functioning,⁶ uremia,⁷ failure of family support, restrictions in daily life, non-compliance to therapeutic regimen including restrictions in diet and fluids, and dependency upon treatment and health professionals.⁸

A study from Brazil showed depression and anxiety symptoms present in 41.7% and 32.3% of dialysis

patients, respectively.⁹ Another study from Nepal showed depression at 75.5% and anxiety at 45.7%.¹⁰ Anxiety and depression are more common in hemodialysis patients, according to a cross-sectional survey done from Pakistan using the HADS scale: 57.30% of their sample had depression, and 42.69% had anxiety disorders.¹¹

The Anxiety and Depression Scale (HADS) was initially developed by Zigmond and Snaith and was applied in many studies.¹²⁻¹⁴ Co-morbidities, recurrent hospital stays and very frequent in dialysis patients.¹⁰ The purpose of this study was to evaluate the levels of anxiety and sadness in dialysis patients.

METHODOLOGY

This descriptive cross-sectional study was conducted at the Department of Nephrology, Chandka Medical College, Larkana from August 2022 to December 2022. The study was approved by the Institutional Research and ethical Review committee of Khairpur Medical College (Ref: KMC/RERC/65 dated 05/10/2022). An informed consent was obtained from all participants.

The sample size of 175 patients was calculated through the standard method. The sampling technique was non-probability consecutive sampling. The patients having age limits between 18 to 60 years and diagnosed cases of

ESRD going for renal dialysis were enrolled. Those patients who had depressive or anxiety disorders before dialysis, those who used any type of psychoactive substance use, and those who had other chronic medical conditions other than chronic kidney disease were excluded from the study.

Depression and Anxiety were assessed as per HADS.¹³ The HADS is a 14-item scale, with seven items relating to anxiety and seven relating to depression. Each item is scored from 0-3 and this means that a person can score between 0 and 21 for either anxiety or depression. Furthermore, Depression and anxiety were categorized and labeled as Normal (0-7 score), Borderline (8-10score), and -Abnormal (11-21) as per HADS.^{13,14}

Statistical Analysis: The data were analyzed by SPSS version 22.

RESULTS

Amongst a total of 175 participants with an average age of 54.26 ± 15.42 years, 65.1% were males and 34.9% females. Among the total, 90.9% were married and 9.1% were single. Demographic characteristics of participants are shown in Table 1. Among total patients undergoing renal dialysis, 100 (57.10%) had this more than one year, 48 (27.40%) were having duration of dialysis of less than one year, and 27 (15.40%) were of less than one-month duration (Fig. 1).

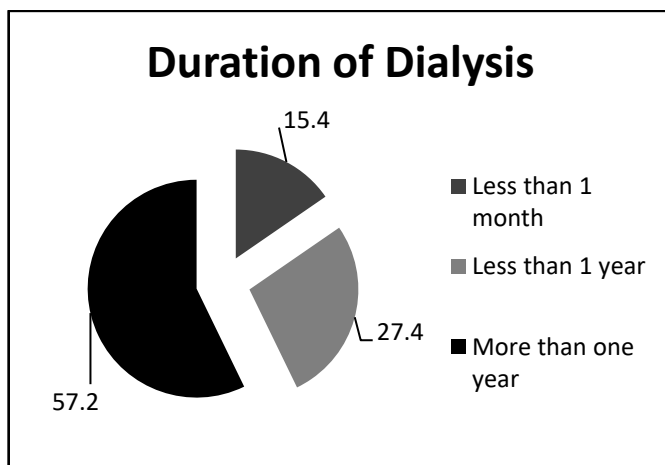


Fig. 1: Frequency according to duration of renal dialysis.

Amongst all, 117 (66.90%) were abnormal for anxiety disorder and 37 (21.10%) were borderline for anxiety disorder while 21(12.0%) were not having anxiety disorder. Depression among patients of dialysis was 92 (52.60%) were abnormal while 48 (27.40%) had borderline depression and 35 (20.0%) were not having depression (Fig. 2). Anxiety and Depression were statistically significantly associated with duration of

dialysis having a p value of 0.019 and 0.001, respectively (Table 2).

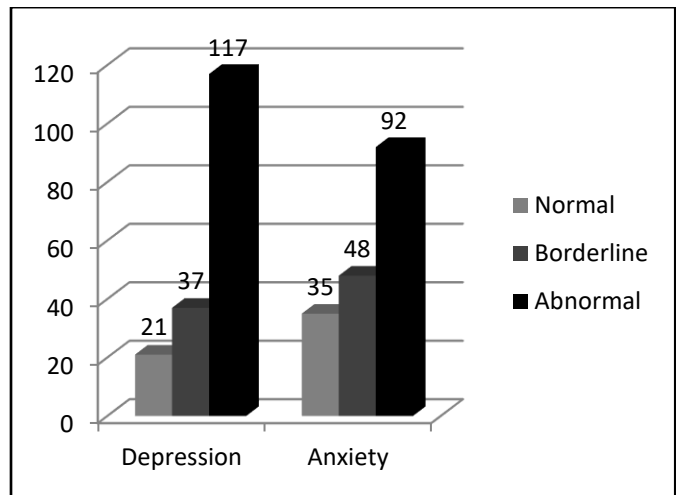


Fig. 2: Frequency of depression and anxiety.

Table 1: Demographic details.

Characteristics	n (%)
Gender	
Male	114(65.1)
Female	61(34.9)
Marital status	
Single	16 (9.10)
Married	159 (90.90)
Education status	
Deeni-Taleem (Religious education)	19 (10.90)
Primary	33 (18.90)
Middle	12 (6.90)
Matric	14 (8.00)
Intermediate	12 (6.90)
Graduate	05 (2.90)
Illiterate	80 (45.70)
Occupation status	
Student	01 (0.60)
Jobless	55 (31.40)
Household	41 (23.40)
Professional	11 (6.30)
Shopkeeper	18 (10.30)
Other Profession	49 (28.00)
Language	
Sindhi	166 (94.90)
Balochi	06 (3.40)
Other	03 (1.70)

DISCUSSION

In this study, 66.9% and 52.6% of patients receiving hemodialysis experienced sadness or anxiety. These

Table 2: Stratification of anxiety and depression with duration of dialysis.

Anxiety Disorder		Normal	Borderline	Abnormal	Total	p-Value
Duration of Dialysis	Up to one month	4 (14.8%)	6 (22.2%)	17 (63.0%)	27 (100.0%)	0.019
	Less than one year	16 (33.3%)	7 (14.6%)	25 (52.1%)	48 (100.0%)	
	More than one year	15 (15.0%)	35 (35.0%)	50 (50.0%)	100 (100.0%)	
	Total	35 (20.0%)	48 (27.4%)	92 (52.6%)	175 (100.0%)	
Depressive Disorder		Normal	Borderline	Abnormal	Total	
Duration of Dialysis	Up to one month	4 (14.8%)	10 (37.0%)	13 (48.1%)	27 (100.0%)	0.001
	Less than one year	7 (14.6%)	0 (0.0%)	41 (85.4%)	48 (100.0%)	
	More than one year	10 (10.0%)	27 (27.0%)	63 (63.0%)	100 (100.0%)	
	Total	21 (12.0%)	37 (21.1%)	117 (66.9%)	175 (100.0%)	

results are comparable to a study from Nepal, which reported that patients with chronic renal disease had a 75.50% prevalence of depression.¹⁵ Another hospital-based study of patients receiving hemodialysis found a prevalence of 78%.¹⁶ The prevalence of depression and anxiety was found to be 66% and 61%, respectively, in a study from Rajasthan, India which is pretty comparable to ours.¹⁷ Another research yielded comparable findings, with anxiety coming in at 68.75% and depression at 77.08%.¹⁸ As a study from Nepal reported the prevalence of depression to be 51.8%, which is lower than this study,¹⁹ several investigations carried out in other regions of the world also indicated lower rates as compared to ours.

A study from Middle East discovered that patients receiving hemodialysis had a prevalence of anxiety and depression of 56.4% and 51.3%, respectively.²⁰ According to research done in Brazil, 41.70% and 32.30% of dialysis patients, respectively, had signs of melancholy and anxiety.²¹

In general, it can be said that a patient with chronic kidney disease receiving dialysis has a high prevalence of anxiety and depression. However, the prevalence of anxiety and depression is seen to vary between different studies conducted primarily due to differences in study design, diagnostic criteria used, study population, and tools used in the study. The literature that is now accessible is inconsistent when it comes to how gender anxiety and depression are related in patients. In this study, more men were enrolled, and greater anxiety was discovered even though, in general, women experience anxiety more frequently.

While there is no link between these factors in other studies,²² certain research has shown a high correlation between them. Furthermore, we found that patients who had been receiving dialysis for more than a year were

more likely to experience melancholy and anxiety.

This study does have some drawbacks. Only the prevalence of the conditions could be examined because this was a descriptive cross-sectional study; associations or correlations between the study variables were not possible. The causation could not be proven in this investigation. Additionally, the study's single-centric focus and small sample size limit how broadly the results may be applied.

CONCLUSION

The study found an alarmingly high frequency of sadness and anxiety among chronic renal disease patients receiving hemodialysis. The result emphasizes the value of early psychiatric assessment and intervention in this population to enhance quality of life.

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REFERENCES

1. Kimmel PL: Psychosocial factors in dialysis patients. *Kidney Int* 2001;59:1599–1613.
2. Goyal E, Chaudhury S, Saldanha D. Psychiatric comorbidity in patients undergoing hemodialysis. *Ind Psychiatry J* 2018;27:206–12.
3. Watnick S, Wang PL, Demadura T, Ganzini L. Validation

- of depression screening tools in dialysis patients. *Am J Kidney Dis* 2005;46:919–24.
4. Fan L, Sarnak M, Tighiouart H, Drew D, Kantor A, Lou K, et al. Depression and all-cause mortality in haemodialysis patients. *Am J Nephrol* 2014;40:12–18.
 5. Jahromi M, Javadpour S, Taheri L, Poorgholami F. Effect of nurse-led telephone follow ups (tele-nursing) on depression, anxiety and stress in hemodialysis patients. *Glob J Health Sci* 2016;8:168–173.
 6. Dijk S, Beukel T, Kaptein A, Honig A, Cessie S, Siegert C, et al. How baseline, new-onset, and persistent depressive symptoms are associated with cardiovascular and non-cardiovascular mortality in incident patients on chronic dialysis. *J. Psychosom Res* 2013;74:511–517.
 7. Chilcot J, Wellsted D, Gane M, Farrington K. Depression on dialysis. *Nephron Clin Pract* 2008;108:256–64.
 8. Vasilopoulou C, Bourtsi E, Giaple S, Koutelekos I, Theofilou P, Polikandrioti M. The Impact of Anxiety and Depression on the Quality of Life of Hemodialysis Patients. *Glob J Health Sci* 2015;8:45–55.
 9. Brito Daniela Cristina Sampaio de, Machado Elaine Leandro, Reis Ilka Afonso, Carmo Lilian Pires de Freitas do, Cherchiglia Mariangela Leal. Depression and anxiety among patients undergoing dialysis and kidney transplantation: a cross-sectional study. *Sao Paulo Med J* 2019;137:137–47.
 10. Kunwar D, Kunwar R, Shrestha B, Amatya R, Risal A. Depression and quality of life among chronic kidney disease patients. *J Nepal Health Res Counc* 2020;14;18:459–65.
 11. Tanvir S, Butt G, Taj R. Prevalence of depression and anxiety in chronic kidney disease patients on hemodialysis. *Ann Pak Inst Med Sci* 2013;9:64–7.
 12. Snaith RP. The hospital anxiety and depression scale. *Health Qual Life Outcome* 2003;1:1–4.
 13. Zahoor F, Nazar Z, Masud S, Rahim R. Relative risk of anxiety and depression among COVID-19 survivor healthcare workers from a tertiary care hospital in Pakistan: A pilot cohort study. *JCPSP* 2021;31:1244.
 14. Aggarwal D, Vaz FS. Psychological Distress among Family Members of Inpatients in General Medicine Wards at a Tertiary Care Hospital: A Cross-sectional Study. *J Clin Diagn Res* 2021;15:5–8.
 15. Gerogianni G, Polikandrioti M, Babatsikou F, Zyga S, Alikari V, Vasilopoulos G, et al. Anxiety–depression of dialysis patients and their caregivers. *Medicina* 2019;55:168–72.
 16. Agrawaal KK, Chhetri PK, Singh PM, Manandhar DN, Poudel P, Chhetri A. Prevalence of depression in patients with chronic kidney disease Stage 5 on hemodialysis at a tertiary care center. *J Nepal Med Assoc* 2019;57:172–5.
 17. Gadia P, Awasthi A, Jain S, Koolwal GD. Depression, and anxiety in patients of chronic kidney disease undergoing haemodialysis: A study from western Rajasthan. *J Family Med Prim Care* 2020;25:4282–6.
 18. Sharma R, Sharma SC, Chalise P, Regmee J, Sharma S. Anxiety and Depression among Patients with Chronic Kidney Disease Undergoing Hemodialysis in a Tertiary Care Centre: A Descriptive Cross-sectional Study. *J Nepal Med Assoc* 2022;1;60:634–7.
 19. Manadhar NR, Shakya R, Pandey B, Wagley P. Depression among patients undergoing maintenance hemodialysis at a tertiary care center in Kathmandu, Nepal. *J Patan Acad Health Sci* 2018;5:4–11.
 20. Jadhav BS, Dhavale HS, Dere SS, Dadarwala DD. Psychiatric morbidity, quality of life and caregiver burden in patients undergoing hemodialysis. *Med J Dr. D.Y. Patil Vidyapeeth* 2014;7:722–7.
 21. Brito DCS, Machado EL, Reis IA, Carmo LPFD, Cherchiglia ML. Depression and anxiety among patients undergoing dialysis and kidney transplantation: a cross-sectional study. *Sao Paulo Med J* 2019;15;137:137–47.
 22. Mosleh H, Alenezi M, Al Johani S, Alsani A, Fairaq G, Bedaiwi R. Prevalence and factors of anxiety and depression in chronic kidney disease patients undergoing hemodialysis: a cross-sectional single-center study in Saudi Arabia. *Cureus* 2020;15;12:e66668.

Evaluating the influence of closed suction system on oxygen saturation, heart rate, and blood pressure in patients with mechanical ventilation

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Objective: To evaluate the influence of closed suction systems on oxygen saturation, heart rate, and blood pressure in patients on mechanical ventilation.

Methodology: This study used a pre-experimental one-group pretest-posttest design in an intensive care unit. A purposive sample of 199 respondents was included. Data collection was from February to April 2024. We recorded oxygen saturation, heart rate, and blood pressure before suctioning, immediately, five minutes, and 15 minutes after suctioning. Data were analyzed using frequency, percentage, Friedman, and Wilcoxon for post hoc analysis.

Results: A closed suction system before suctioning, immediately after suction, five minutes after suction, and 15 minutes after suction showed mean oxygen

saturation was 92%, 94%, 96%, and 98%; heart rates per minute were 108, 109, 100, and 93; and blood pressure (systolic/diastolic mmHg) was 125/77, 128/79, 121/77, and 118/76. The Friedman test showed significant differences in SpO₂, heart rate, and blood pressure between before and immediately after suctioning, five minutes after suctioning, and 15 minutes after suctioning (p=0.001).

Conclusion: The application of closed suction system in the ICU showed promising results in maintaining the hemodynamic status of patients with mechanical ventilation.

Keywords: Closed suction, oxygen saturation, blood pressure, heart rate.

INTRODUCTION

Artificial airway management is an essential treatment for critically ill patients. It ensures the airway remains clear of secretions and avoids infections that can narrow or even close the airway completely.¹ Airway management is one of the cores of critically ill patients' care, aiming to maintain the airway.² One of the criteria for critically ill patients to be admitted to the intensive care unit (ICU) is requiring intensive therapy and ventilator support.³

Critically ill patients in the ICU are often placed on ventilators so that they require suctioning to clear the airway from secretions. Patients are suctioned 8-17 times daily. Suctioning can be done with an open suction system (OSS) and a closed suction system (CSS).⁴ OSS removes the ventilator circuit and inserts a catheter.⁵ Suctioning should be performed when the patient's oxygen saturation (SpO₂) is less than 95%, even though hyperoxygenation has been performed, as mucus has impeded airflow. The recommended suction pressure is 100 mmHg because it can suck mucus and, at the same time, reduce the risk of decreased oxygen saturation due to suctioning.³

In CSS, suctioning is performed on patients attached to mechanical ventilation without removing the ventilator

circuit. It has the advantages of maintaining positive expiratory final pressure, oxygen intake, and positive ventilation. The cannula on CSS is never detached with a ventilator. Thus, during operation, the airflow continues to run smoothly without interruption.³ In OSS, a suction catheter is inserted into the artificial airway.⁴ Due to endotracheal intubation and mechanical ventilation, the mucociliary ability to clear the airway becomes impaired. Therefore, endotracheal tube suctioning is necessary for intubated patients in the ICU to remove mucus from the airway,⁶ avoid complications such as atelectasis, and maintain oxygenation.⁷

One of the roles of ICU nurses in patients attached to mechanical ventilation is to perform tracheal suctioning to remove secretions to prevent airway obstruction and patient discomfort.⁸ Therefore, this study aimed to evaluate the influence of CSS on oxygen saturation, heart rate, and blood pressure in patients with mechanical ventilation in the intensive care unit Haji Adam Malik Hospital, Medan, Indonesia.

METHODOLOGY

This study used a pre-experimental design in the ICU of Haji Adam Malik Hospital Medan, North Sumatra province, Indonesia. The period of data collection was

from February to April 2024. The study received permission through an official letter from the research ethics committee of the Universitas Sumatera Utara Number 95/KEPK/USU/2024, and all respondents' family members signed informed consent.

The sample size was calculated using G*Power software version 3.1. With an effect size of 0.2, error probability of 0.05, and power of 0.8, a sample of 199 respondents was obtained by using purposive sampling. The inclusion criteria were; 1) compos mentis to coma level of consciousness; 2) closed suction connected via endotracheal tube ventilator for at least 24 hours; and 3) adult patients. The exclusion criteria were; 1) patients under 18 years of age; 2) patients with tracheostomy; and 3) patients with pulmonary tuberculosis.

The instrument used in this study was an observation sheet to record oxygen saturation, heart rate, and blood pressure before suctioning, immediately after suctioning, five minutes after suctioning, and 15 minutes after suctioning. The CSS used was a Hitecare (Hitec Medical Co., Ltd.-China), and the monitor to measure oxygen saturation, heart rate, and blood pressure was a Dixon Storm 5900-02 (Dixon Vertrieb medizinischer Geräte GmbH-Germany).

Statistical Analysis: Data analysis used univariate, bivariate, and multivariate. SpO₂, heart rate, and blood pressure data were analyzed using the Friedman test because the data did not fulfill the assumption of normally distributed, followed by post hoc analysis using the Wilcoxon test. The difference was statistically significant if p value was less than 0.05.

RESULTS

There were 199 respondents involved in the study, with a mean age of 52 years. Table 1 shows that many respondents were aged 55-71 years, 80 (40.2%), men 113 (56.8%), did not smoke 119 (59.8%), and had a high school education level 137 people (68.8%). The mean oxygen saturation before suctioning was 92% and increased successively immediately after suctioning (94%), five minutes after suctioning (96%), and 15 minutes after suctioning (98%). Regarding heart rate, the mean before suctioning was 108 times per minute and increased immediately after suctioning to 109, decreased five minutes after suctioning to 100, and decreased 15 minutes after suctioning to 93.

The mean systolic BP before suctioning was 125 mmHg and increased immediately after suctioning 128 mmHg, decreased at five minutes after suctioning 121 mmHg, and decreased again 15 minutes after suctioning 118 mmHg. The mean diastolic BP before suctioning measures 77 mmHg, increased immediately after suctioning 79 mmHg, decreased five minutes after

suctioning 77 mmHg, and decreased 15 minutes after suctioning 76 mmHg. The results of multivariate data analysis using the Friedman test found significant differences in SpO₂, heart rate, and blood pressure before and immediately after suctioning, five minutes after suctioning, and fifteen minutes after suctioning (Table 2).

Table 1: Socio-demographic information of respondents (n=199).

Characteristic	Frequency	%
Age (years)		
19-36	34	17.1
37-54	73	36.7
55-71	80	40.2
72-88	12	6
Smoke		
Yes	80	40.2
No	119	59.8
Gender		
Men	113	56.8
Women	86	43.2
Education		
Elementary	7	3.5
Middle school	23	11.6
High school	137	68.8
Diploma	10	5
Bachelor	22	11.1
Employment		
Unemployed	23	11.6
Government employee	9	4.5
Private Employee	37	18.6
Farmer	35	17.6
Merchant	6	3
Driver	1	0.5
Other	88	55.8

The post hoc analysis results using the Wilcoxon signed ranks test showed that oxygen saturation and heart rate differed significantly between before and immediately after suctioning, five minutes after suctioning, and 15 minutes after suctioning. Systolic blood pressure also differed significantly between before suctioning and immediately and five minutes after suctioning. In contrast, diastolic blood pressure differed significantly only between before suctioning and immediately after suctioning (Table 3).

DISCUSSION

This study found significant differences in SpO₂, HR, and BP before suctioning compared to immediately after suctioning, five minutes after suctioning, and 15 minutes after suctioning, with a p-value of 0.001, as shown in

Table 2. Jongerdan et al,⁹ showed a change in mean blood pressure, heart rate, and SpO₂ immediately after suctioning and reached baseline values five minutes after suctioning.

The study compared the OSS with the CSS by measuring four times, namely before suctioning, immediately after suctioning, three minutes after suction, and five minutes after suction. CSS cause fewer physiological complications.⁵ They are the best option for critically ill patients in the ICU. Compared to OSS, CSS cause less interference with cardiorespiratory parameters such as respiratory rate, SpO₂, heart rate, and mean arterial blood pressure.¹⁰ The results of a randomized

controlled trial study showed that compared to standard suction, CSS can reduce secretion accumulation and bacterial thickness in ICU patients.¹

Theoretically, some advantages of using CSS are less SpO₂ decrease, more

stability in maintaining positive end-expiratory pressure (PEEP), less lung volume loss,¹¹ and a reduction in pain levels.² Maggiore et al,¹² found that in patients with ARDS, there was a significantly lower decrease in pulmonary gas volume in CSS compared to OSS. A systematic review found that the decrease in SpO₂ in CSS was much lower immediately after suctioning than in OSS.¹³

CSS provides several benefits to patients, such as suctioning can be done by a nurse without assistance, suctioning is completed faster, the risk of hemodynamic disorders at the time of suctioning is reduced, particles are prevented from leaking, mucus is prevented from spreading into the atmosphere, and transmission to nurses or other patients is prevented. Other benefits are that patients stay connected to the ventilator so that ventilation continues during suctioning, and patients feel calmer and more cooperative.⁵ In addition, CSS can

Table 2: SpO₂, heart rate, and blood pressure before suctioning, immediately, five minutes, and 15 minutes after suctioning (n=199).

Variable	SpO ₂	Heart Rate	BP Systolic	BP Diastolic
Before suctioning				
- Min – Max	88 – 95	46 – 155	70 – 190	40 – 102
- Mean (SD)	92 (1.4)	108 (16)	125 (20)	77 (13)
Immediately after suctioning				
- Min – Max	89 – 97	60 – 157	74 – 180	45 – 110
- Mean (SD)	94 (1.3)	109 (16)	128 (20)	79 (12)
Post-suctioning 5th minutes				
- Min – Max	90 – 99	50 – 150	70 – 170	42 – 100
- Mean (SD)	96 (1.5)	100 (14)	121 (17)	77 (11)
Post-suctioning 15th minutes				
- Min – Max	85 – 100	47 – 145	72 – 165	50 – 100
- Mean (SD)	98 (1.9)	93 (15)	118 (15)	76 (9)
^a p-value	0.001	0.001	0.001	0.001

^aFriedman test

Table 3: Post hoc analysis (Wilcoxon signed ranks test) of the differences in SpO₂, heart rate, and blood pressure: before suctioning, immediately, five minutes, and 15 minutes after suctioning (n=199).

Variable	Immediately after suctioning	Post-suctioning 5 th minutes	Post-suctioning 15 th minutes
	p-value	p-value	p-value
SpO ₂ , before suctioning	0.001	0.001	0.001
Heart rate before suctioning	0.014	0.001	0.001
BP systolic, before suctioning	0.001	0.001	0.226
BP diastolic, before suctioning	0.001	0.594	0.135

reduce the negative impacts of suctioning, such as hypoxemia and environmental contamination.¹⁴

CONCLUSION

The application of a closed suction system in the ICU showed promising results in maintaining some hemodynamic status of patients with mechanical ventilation after 15 minutes. Therefore, all healthcare providers, including nurses, must maintain the continuity of ventilator function available at Haji Adam Malik Hospital.

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REFERENCES

1. Kaur R, Scott JB, Weiss TT, Klein A, Charlton ME, Villanueva KA, et al. Evaluation of a closed suction system with integrated tube-scraping technology. *Respir Care* 2023;68:1023–30.
2. Deng J, Huang S, Zou D, Liu W, He M, Xiong J, et al. Investigation of the airway management practice of emergency department ward nurses: a nationwide survey in China. *BMJ Open* 2021;11:e049869.
3. Widodo S, Daya D, Armiyati Y, Mustofa A, Machmudah M, Poddar S. Techniques closed suction influence on oxygen saturation in patients using mechanical ventilation in intensive care unit room. *Malaysian J Med Heal Sci* 2020;16:102–5.
4. Stilma W, Esmeijer A, Paulus F, Frenzel T, Touw H, Stobernack T. Open versus closed suctioning in Invasively ventilated critically ill patients for sustainability of ICU care: A life-cycle assessment comparison. *Respir Care* 2024;69:218–21.
5. Dastdadeh R, Ebadi A, Vahedian-Azimi A. Comparison of the Effect of Open and Closed Endotracheal Suctioning Methods on Pain and Agitation in Medical ICU Patients: A Clinical Trial. *Anesthesiol Pain Med* 2016;6:1–8.
6. Dexter AM, Scott JB. Airway management and ventilator-associated events. *Respir Care* 2019;64:986–93.
7. Yildirim S, Saygili SM, Süneçli O, Kirakli C. Comparison of the effects of open and closed aspiration on end-expiratory lung volume in acute respiratory distress syndrome. *Korean J Anesthesiol* 2024;77:115–21.
8. Ramírez-Torres CA, Andrade-Gómez E, Giménez-Luzuriaga M, Lozano C, Sapiña-Beltrán E. Closed suction system in tracheal suctioning in the critically ill patient connected to mechanical ventilation: A systematic review. *Arch Bronconeumol* 2024;60:116–8.
9. Jongerden IP, Kesecioglu J, Speelberg B, Buiting AG, Leverstein-van Hall MA, Bonten MJ. Changes in heart rate, mean arterial pressure, and oxygen saturation after open and closed endotracheal suctioning: A prospective observational study. *J Crit Care* 2012;27:647–54.
10. Mulla RJ, Mohite VR. Efficacy of Closed and Open Endotracheal Suction on Prevention of Ventilator-Associated Pneumonia on Patients Admitted to Critical Care Unit at Tertiary Care Hospital. *J Datta Meghe Inst Med Sci Univ* 2023;18:192–8.
11. Chiumello D, Bolgiaghi L, Formenti P, Pozzi T, Lucenteforte M, Coppola S. Effects on lung gas volume, respiratory mechanics and gas exchange of a closed-circuit suctioning system during volume- and pressure-controlled ventilation in ARDS patients. *J Clin Med* 2021;10:5657.
12. Maggiore SM, Lellouche F, Pigeot J, Taille S, Deye N, Durrmeyer X, et al. Prevention of Endotracheal Suctioning-induced Alveolar Derecruitment in Acute Lung Injury. *Am J Respir Crit Care Med* 2003;167:1215–24.
13. Solà I, Benito S. Closed tracheal suction systems versus open tracheal systems for mechanically ventilated adult patients. *Cochrane Database Syst Rev* 2007;2007:CD004581.
14. Jung F, Chou SSP, Yang SH, Lin JC, Jow GM. Optimizing effects on airway pressure and minute volume during closed endotracheal suctioning: a simulated lung model. *Simulation [Internet]*. 2021;97:439–49.

Prevalence of common mental illness and associated risk factors in patients reporting in DHQ hospital, Gilgit Baltistan

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Objective: To determine the prevalence of various mental illness in patients reporting to DHQ Ghizer, Gilgit Baltistan and examine their associated risk factors, along with suicidal ideations and suicidal attempts.

Methodology: The study included 749 individuals seeking attention for psychiatric disorders at Ghizer-DHQ Hospital. They were assessed based on the guidelines provided by the International Classification of Diseases-10 (ICD-10).

Results: Out of 749 individuals, 47.3% received a diagnosis of depressive episode, 12.7% were diagnosed

with generalized anxiety disorder and 8.9% with recurrent depressive disorder. We found 154 cases had a positive family history of psychiatric illness followed by death of loved ones. Individuals who confirmed suicidal ideations were 268, while about 127 were those who had attempted suicide previously.

Conclusion: Significant number of patients had anxiety and depression. The results highlight the need for holistic and individualized approaches to mental health care.

Keywords: Mental illnesses, depressive disorder, suicide.

INTRODUCTION

A mental disorder is defined as a significant disruption in an individual's cognitive functions, emotional regulation, or behavioural patterns.¹ The prevalence of mental illnesses is increasing on a global scale. In 2019, approximately 1 out of every 8 individuals worldwide was reported to be grappling with depressive or anxiety disorders.² This number escalated by nearly 26% in the first year of the Covid-19 pandemic.^{3,4} Nearly 50 million Pakistanis are affected by some form of mental disorder, with 10% requiring attention for mental health issues and astonishingly, the country has fewer than 500 psychiatrists.^{3,4}

Despite this, there hasn't been an epidemiological study to establish the true prevalence of mental disorders and their associated factors. The most commonly associated risk factors worldwide encompass family history (genetic predisposition), poverty (financial difficulties), loss of loved ones, traumatic experiences, substance abuse, and childhood abuse.^{7,8} An older systematic review suggested that factors like being female, having lower education, being of middle age, experiencing the loss of a spouse, and being a homemaker were associated with anxiety and depressive disorders in Pakistan.⁹ This study aimed to assess the prevalence of various mental illnesses while also examining their associated risk factors, along with suicidal ideations and suicidal attempts in Gilgit

Baltistan.

METHODOLOGY

This cross-sectional study was conducted from June to December 2022 at DHQ Hospital in Ghizer, Gilgit Baltistan. The study was approved by IRB and Medical Superintendent of the Hospital (Letter no.1501/MS-DHQ/Estb/2015). An informed consent was taken from all participants. For children the consent was taken from their guardian/parents.

The research focused on consecutive patients aged between 12 and 90 of both genders. A structured questionnaires were employed to gather comprehensive information. Diagnosis of illnesses for adolescents and adults was carried out by Adult and Adolescent Psychiatrist. The diagnosis for children was carried out by a psychiatrist with experience in Child psychiatry adhering to the guidelines outlined in the International Classification of Disease-10 (ICD-10).

Statistical Analysis: The data were analyzed by SPSS version 22.

RESULTS

Out of 749 individuals, 354 (47.3%) received a diagnosis of depressive episode. Following this, 12.7% were diagnosed with generalized anxiety disorder (GAD),

8.9% with recurrent depressive disorder, and 6.9% had a concurrent diagnosis of mixed anxiety and depressive disorder. Among anxiety disorders, after GAD the second most common disorder was panic disorder present in 3.9%.

Furthermore, there were 28 cases (3.7%) of bipolar affective disorder, 29 (3.3%) of schizophrenia, 14 (1.9%) had mental and behavioral disorders linked to psychoactive substances, 2 (0.3%) were associated with the postpartum period, and another 2 (0.3%) had somatization disorder. Schizophrenia was diagnosed in 25 cases.

The most prevalent associated factor in these cases was a family history, identified in 10 cases (Table 1 and 2). Among those 14 individuals suffering from mental and behavioral disorders associated with psychoactive substances, stress related to studies or work emerged as the most common factor, affecting 3 cases.

Suicidal ideation and attempts were common (Table 3). Twelve cases were diagnosed with adjustment disorder. Among this group, 3 cases were connected to the death of parent(s), 2 cases to the death of a sibling, and 2 cases to early or forced marriage. In cases of acute stress disorder, 2 cases each were associated with being flood survivors, the death of a sibling, and the death of parent(s). Anxiety disorders and the risk factors linked to it are shown in Table 4.

DISCUSSION

In this study, predominant presence of female participants is similar to the findings of previous studies,¹⁰ and corresponds to the notion that women tend to engage in rumination more frequently than men.¹¹ The study also sheds light on a potential gender-based discrepancy in seeking mental health assistance.¹⁰ Various prevalent psychiatric disorders were identified among the participants in the study. These findings are similar to several other studies.^{14,15}

Diverse factors were unraveled, including family history and experience of losing loved ones alongside prevalent contributors like domestic issues, health concerns of self and family members and financial issues. Remarkably, these findings align with previous studies,^{14,15} underscoring the

Table 1: Risk factors associated with various illnesses.

Categories	N	%
Family history	154	20.8
Death of loved ones	119	15.8
Domestic issues	87	11.6
Health Issues of self/family	82	10.9
Financial issues as first reason (Total 113, 15.1%)	67	8.9
Domestic violence	38	5.1
Stress related studies/work	35	4.7
None	31	4.1
Early/Forced Marriage	24	3.2
Conflicts	22	2.9
Drug Abuse	13	1.7
Jobless	12	1.6
Flood Survivor	11	1.5
Only female children	11	1.5
More children to take care	10	1.3
Husband Away/remarried	8	1.1
Issueless	7	0.9
Personality traits	6	0.8
Over pampered	5	0.7
childhood sexual abuse	1	0.1
Others	6	0.8

Table 2: Depressive disorders and the risk factors linked to it.

Associated risk factor	Depressive Episode		Recurrent Depressive Disorder	
	N	%	N	%
Family history	71	20.0	15	22.4
Death of loved ones	63	17.8	15	22.4
Domestic issues	44	12.4	8	11.9
Health Issues of self/family	41	11.6	6	9.0
Financial issues	25	7.1	11	16.4
Death of Parent/s	17	4.8	5	7.5
Domestic violence	21	5.9	2	3.0
Stress related studies/work	18	5.1	1	1.5

consistent role of Domestic violence analysis revealed that among these, 23 cases were associated with depressive disorders, including 2 cases with recurrent depressive episodes. Additionally, 16 cases showed indications of various anxiety-related conditions, like GAD, with a mixture of anxiety and depression and panic disorder. These findings underscore the urgency of implementing social initiatives in these regions to raise awareness that domestic violence is a major factor in triggering mental illnesses among females.

Domestic issues often hinge upon the cultural context of the society in which individuals reside. In this regard, prevalent domestic concerns include situations like husbands living separately, sons residing away for reasons like education or family conflicts, conflicts arising with husbands or extended family members such as mothers-in-law. Issues extending to divorce, disputes within the paternal or maternal family spheres concerning property matters, and instances of being involved in extramarital relationships or experiencing betrayal within such relationships.

Less frequently encountered yet noteworthy associated factors included drug abuse, unemployment, excessive pampering, grappling with childlessness, contending with either solely female offspring or managing a larger number of children, among others. These factors remain significant contributors to social issues that can potentially impact the mental well-being of residents within this specific region.

The findings of this study have several implications. They underscore the importance of understanding the diversity of the underlying factors that contribute to the development and severity of mental illnesses and highlights the need for genetic research, tailored interventions, and support systems to address these multifaceted challenges effectively. The study's scope was limited to a specific hospital and region, potentially limiting the generalizability of the findings. Additionally, the study did not explore potential causality between risk factors and disorders, warranting further research to

Death of Partner	24	6.8	3	4.5
None	5	1.4	0	0.0
Death of Child	12	3.4	6	9.0
Early/Forced Marriage	15	4.2	2	3.0
Conflicts	14	4.0	1	1.5
Death of siblings	10	2.8	1	1.5
Drug Abuse	5	1.4	0	0.0
Jobless	4	1.1	0	0.0
Only female children	4	1.1	2	3.0
Flood Survivor	3	0.8	2	3.0
More children to take care	7	2.0	0	0.0
Husband Away/remarried	3	0.8	1	1.5
Issueless	6	1.7	0	0.0
Personality traits	2	0.6	0	0.0
Others	1	0.3	1	1.5
Over pampered	1	0.3	0	0.0
childhood sexual abuse	1	0.3	0	0.0
Total	354	100	67	100.0

Table 3: Number of cases of suicidal ideations and suicidal attempts.

Variable	N	%
Suicidal ideation	268	35.8
Suicidal attempt	127	17.0

Table 4. Anxiety disorders and the risk factors linked to it.

Associated risk factors	GAD		Mixed Anxiety and Depressive Disorder		Panic Disorder	
	N	%	N	%	N	%
Domestic issues	18	18.6	7	13.6	1	3.4
Health Issues of self/family	19	20.0	9	17.3	0	0.0
Financial issues	14	14.7	7	13.6	3	10.4
Family History	6	6.3	0	0.0	3	10.4
Death of Parent/Parents	2	2.1	2	3.8	3	10.4
Domestic violence	7	7.4	6	11.6	3	10.4
Stress related studies/work	5	5.3	2	3.8	2	6.9

understand the intricate relationships.

CONCLUSION

The results of this study emphasize the complexity of mental health issues, highlighting the need for holistic and individualized approaches to mental health care. The findings contribute to the growing body of knowledge on psychological well-being and serve as a foundation for future research and intervention strategies.

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Death of Partner	4	4.2	2	3.8	1	3.4
None	4	4.2	1	1.9	7	24.3
Death of Child	1	1.1	6	11.6	1	3.4
Early/Forced Marriage	1	1.1	1	1.9	0	0.0
Conflicts	3	3.2	2	3.8	1	3.4
Death of siblings	0	0.0	1	1.9	0	0.0
Drug Abuse	1	1.1	1	1.9	1	3.4
Jobless	3	3.2	1	1.9	0	0.0
Only female children	0	0.0	0	0.0	1	3.4
Flood Survivor	3	3.2	0	0.0	0	0.0
More children to take care	0	0.0	2	3.8	0	0.0
Husband Away/remarried	2	2.1	1	1.9	1	3.4
Issueless	1	1.1	0	0.0	0	0.0
Personality traits	0	0.0	1	1.9	0	0.0
Others	1	1.1	0	0.0	0	0.0
Over pampered	0	0.0	0	0.0	1	3.4
Death of loved ones	7	7.4	11	21.1	5	17.2
Total	95	100	52	100	29	100.0

GAD: generalized anxiety disorder; (Deaths of loved ones = all deaths counted together)

REFERENCES

1. WHO. Mental disorders 2022 [Available from: <https://www.who.int/news-room/fact-sheets/detail/mental-disorders>.
2. WHO. Mental Health and Covid-19: Early evidence of the pandemic's impact: Scientific brief, 2 March 2022. 2022.
3. Reporter S. 50m Pakistanis suffering from mental disorders. DAWN. 2016 October 9, 2016.
4. Sikander S. Pakistan. Lancet Psychiatry 2020;7:845-7.
5. Riaz M, Abid M, Bano Z. Psychological problems in general population during covid-19 pandemic in Pakistan: role of cognitive emotion regulation. Ann Med 2021;53:189-96.
6. Ali DA, Ali IA, Sakharani K, Rohra N. Prevalence of post-traumatic stress disorder among the general population of Karachi during Covid-19 pandemic and its associated factors. J Med 2022;23:36-41.
7. Shah SM, Sun T, Xu W, Jiang W, Yuan Y. The mental health of China and Pakistan, mental health laws and Covid-19 mental health policies: a comparative review. Gen Psych 2022;35(5):e100885.
8. Litin SC. Mental Illness, Symptoms and causes. Mayo Clinic Family Health Book. 5th ed: Recorded Books Audio; 2020.
9. Mirza I, Jenkins R. Risk factors, prevalence, and treatment of anxiety and depressive disorders in Pakistan: systematic review. BMJ 2004;328:794-7.
10. Eaton NR, Keyes KM, Krueger RF, Balsis S, Skodol AE, Markon KE, et al. An invariant dimensional liability model of gender differences in mental disorder prevalence: evidence from a national sample. J Abnorm Psychol 2012;121:282-5.
11. Nolen-Hoeksema S, Wisco BE, Lyubomirsky S. Rethinking rumination. Pers Psychol Sci 2008;3:400-24.
12. Garima M, Kiran U. Impact of marital status on mental health of working women. J Med Sci Clin Res 2014;2:2594-605.
13. Araya R, Lewis G, Rojas G, Fritsch R. Education, and income: which is more important for mental health? J Epidemiol Comm Health 2003;57:501-5.
14. Ormel J, Petukhova M, Chatterji S, Aguilar-Gaxiola S, Alonso J, Angermeyer MC, et al. Disability and treatment of specific mental and physical disorders across the world. BJP 2008;192:368-75.
15. Struijs SY, de Jong PJ, Jeronimus BF, van der Does W, Riese H, Spinhoven P. Psychological risk factors and the course of depression and anxiety disorders: A review of 15 years NESDA research. J Affect Disord 2021;295:1347-59.

Risk factors causing acne & psychosocial effects of acne on medical students

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Objective: To determine factors that affect acne and psychosocial effects of acne on medical students.

Methodology: This cross-sectional study was conducted during the academic year of 2023 and included 220 MBBS students at Al-Nafees Medical College, Islamabad. Students of both gender of all five years of MBBS classes participated in the study. We used a structured, self-administered questionnaire.

Results: Out of 220 students, 99 (45%) were males and 121 (55%) females. The maximum frequency of acne was at 22 years of age. A total of 183 participants had acne, out of which 105 (57.4%) were females. The prevalence rate of acne was 83.2%. Acne was associated with stress in 77 (42.1%) participants. Most with acne 65 (35.5%) consumed chicken frequently, 17 (9.3%) affected with acne drank less than 2 glass waters

daily and 54 (51.4%) used cosmetics on daily basis. Among 105 acne affected females, 25 (23.8%) had excessive hair growth on face and 45 (42.8%) had menstrual flare up. Among acne-affected participants, 78 (42.6%) perceived stress due to acne. In 59 (32.2%) participants, acne affected their confidence level.

Conclusion: The prevalence rate of acne in medical students was 83.2%. Excessive use of cosmetics, decreased water intake and large portions of processed and farm chicken in diet were the leading modifiable factors that require attention. Of those suffering from severe acne, significant increase in stress levels was noted, which forms a vicious cycle, leading to further worsening of acne.

Keywords: Risk factors, causing acne, psychosocial effects, medical students.

INTRODUCTION

Acne vulgaris is a chronic dermatological disease characterized by inflammatory changes in the pilosebaceous glands of the skin resulting in the formation of comedones, pustules, papules, nodules, and cysts.¹ Acne represents the top three most prevalent skin conditions regardless of socioeconomic status, nationality or gender.² It is a common skin condition, which affects most adolescents at some point in their lives.³ The Global Burden of Disease project has estimated the prevalence of acne to be 9.4%, ranking it as the eighth most prevalent disease worldwide.¹

Acne and its sequelae can affect many domains of life leading to social dysfunction, psychiatric issues and educational shortcomings.⁴ It has greater adverse effect on mood than other chronic cutaneous disorders such as psoriasis or alopecia.⁵ Moderate to severe acne greatly affects the quality of life with reduced self-esteem, marred physical appearance and less social relationships with others.⁶ Patients often experience great physical and mental stress especially among the college students, due to its recurrence and scars or post-inflammatory hyperpigmentation left after healing.⁷ Effective treatment of acne was accompanied by improvement in self-esteem, affect, obsessive-compulsiveness, shame, embarrass-

ment, body image, social assertiveness and self-confidence.⁸

Acne and its impact have been well-researched and studied in various parts of the world, including the USA, Europe, and Korea. However, data from Southeast Asian countries like Pakistan remains scanty.¹ Misconceptions exist in the community regarding factors that exacerbate acne vulgaris. Stress, diet, lifestyle, and personal hygiene are often erroneously claimed to be important factors.⁹ Underestimating the severity and progression of acne may delay treatment, while misinterpreting the etiology of acne could lead to unnecessary and disruptive lifestyle changes.¹⁰ The aim of this study was to determine factors that affect acne and psychosocial effects of acne on medical students.

METHODOLOGY

This cross-sectional study was conducted during the academic year of 2023, and included 220 MBBS students at Al-Nafees Medical College, Islamabad. Ethical approval was taken from the ethical review board at HBS (Ref: Appl#ERC dated May 25, 2023) and informed consent was obtained by all participants before conducting the study. Students of both gender of all five years of MBBS participated in the study. Exclusion

criteria were students with any other skin condition which can act as confounding factor.

The sample size was calculated with Raosoft sample size calculator. Data was collected randomly by using a structured, self-administered questionnaire, which was designed after reviewing the recent literature and similar questionnaires. It was divided into two parts. The first part included the sociodemographic data and second part included questions about the factors that cause acne, hormonal imbalance, and the psychosocial effects of acne on the participants.

The questionnaire was validated and modified in the light of a pilot study. The pilot study was conducted on 20 medical students (apart from the target group) to check the understanding and clarity of the questionnaire. The questionnaire was reviewed by 2 researchers before and after the pilot study with minor linguistic modifications of some confusing words. The questionnaires were distributed, explained to participants, and collected after being filled. The Perceived Stress Scale was used to determine stress.

Statistical Analysis: The data were analyzed using SPSS version 22.

RESULTS

Out of 220 students, 99 (45%) were males and 121 (55%) females. Mean age of participants was 21.6 ± 1.6 years. Most were unmarried 95.5% ($n=210$), and 114 (51.8%) were day scholars. We found that 183 (83.2%) participants suffered from acne out of which 105 (57.4%) were females (Table 1). Modal age of students experiencing acne was 22 years. BMI ranged from 15.4-34.9 with a mean of 22.3 ± 3.4 among students suffering from acne.

Acne was present on the face in 125 (68.3%) students, on forehead in 35 (17.5%), on back in 22 (12%) and on neck in 4 (2.2%) students. 74.3% of acne sufferers ($n=136$) had oily skin. Among acne affected participants, 78 (42.6%) perceived moderate to high stress due to acne. It affected the medical school and work performance in 14 (7.7%) participants and friendships were affected in 13 (7.1%) individuals (Fig.1).

We found that 68% students who had acne developed complications (Fig. 3). Cosmetics were used on daily

Table 1: Prevalence rate of acne among respondents.

Number of Participants	Affected with Acne	Not Affected with Acne
220	183 (83.2%)	37 (16.8%)

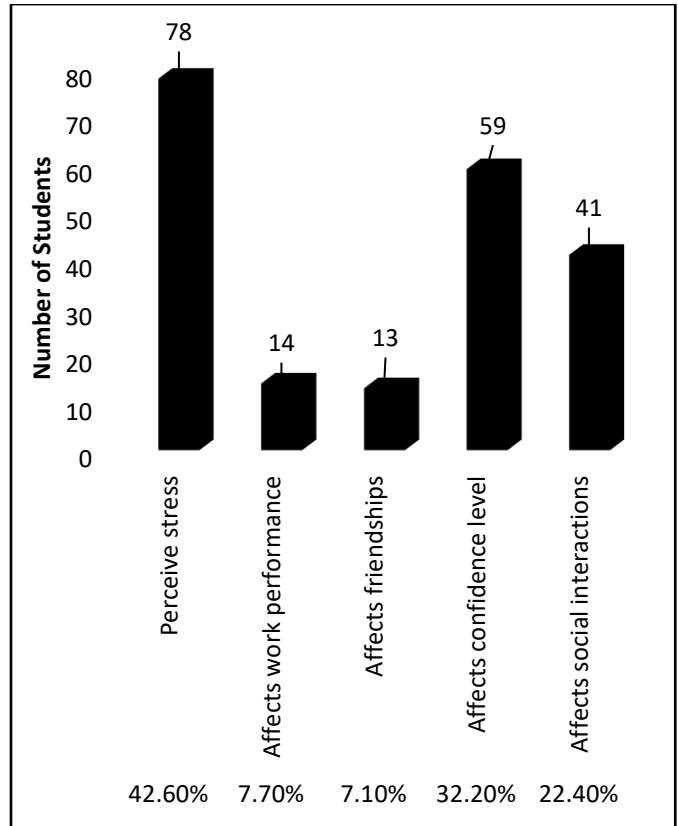


Fig. 1: Psychosocial effects of acne.

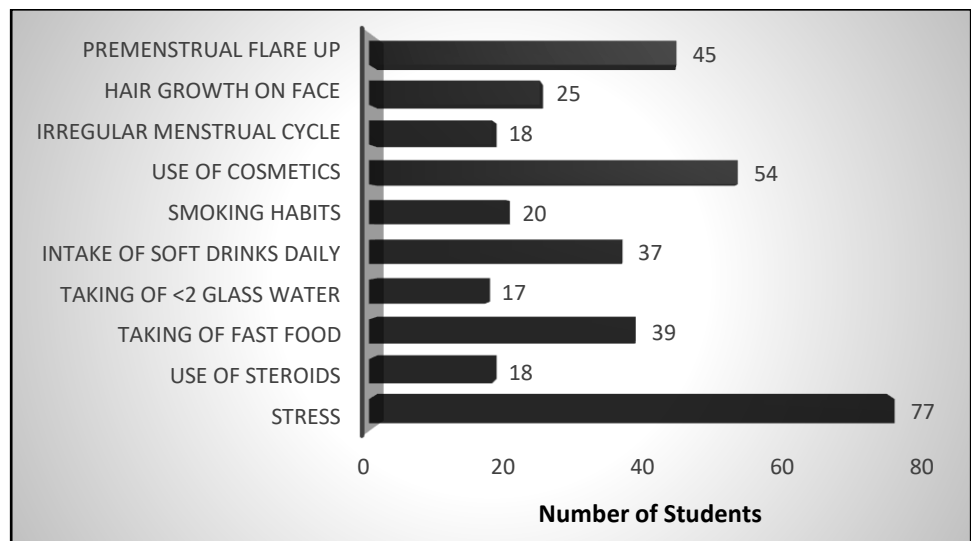


Fig. 2: Factors aggravating /influencing acne.

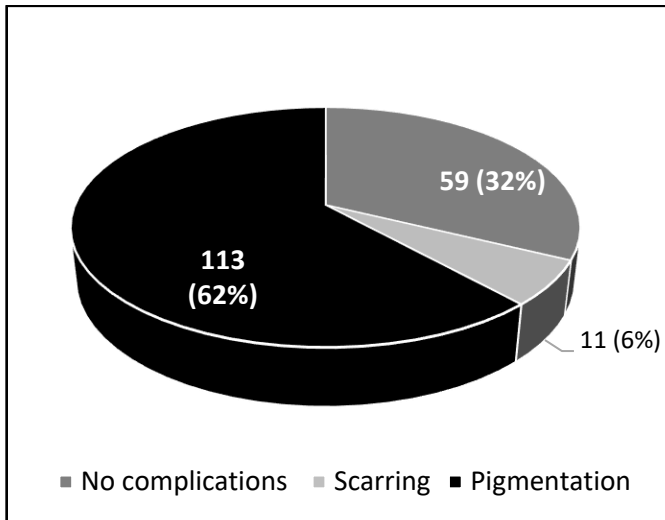


Figure 3: Complications of acne.

basis by 54 (51.4%). Excessive hair growth on face and menstrual flare up were noted (Fig. 2).

DISCUSSION

Our study was exclusively based on students from ISRA University Islamabad, Pakistan, and showed a prevalence of acne of 83.2% in students of an average age of 21 years. This figure agrees with a study done in João Pessoa, which showed an incidence of 89.3%.¹¹ However, studies from other parts of the world showed lower prevalence. Research from Sohag province, upper Egypt showed 33.5% prevalence of acne vulgaris in teenaged students,¹² while a study from China showed that 10.4% college students were affected by acne.³ A study from Saudi Arabia reported that 53.5% students were affected by acne.¹³ In Malaysia, the prevalence among medical students was 68.1%.¹⁴

A common trait seen across many countries is the higher incidence of acne in females as compared to male students.¹² Results from Serbia showed that amongst the population affected by acne, 84.3% were girls and 15.7% were boys.¹⁵ Similarly, our research showed that 57.4% students who suffered from acne were female.

Regarding the grade of acne, we found that most students suffered from grade 1 acne (50.80%), followed by grade 2 acne and grade 3 acne, (28.48% and 14.24%, respectively). This is like the results obtained in studies done in the Nigerian youth where 93.1% had mild acne and only 26 of the 379 students (6.9%) had moderate disease.¹⁶

We found that psychological stress was the commonest factor influencing acne (42.1%), followed by frequent use of cosmetics (54%), premenstrual flare up (45%) and intake of fast food (39%). Most of our participants (42%)

reported to have perceived a lot of stress due to acne, had noticed a decline in their confidence levels and faced difficulties in social interaction. A small proportion also claimed that acne had an adverse effect on their friendships and work efficiency. A Nepalese study showed that 31.2% of surveyed students felt a lack of confidence, while 73.6% students in a Saudi Arabian study believed acne impacted their self-confidence.

A study from Somalia showed that 63% women with acne were under stress and analyzed that stress and premenstrual flare had an important connection with acne.¹⁷ The association between stress and worsened acne remained significant even after controlling for changes in diet and sleep habits in detailed research conducted on university students.¹⁸ The diet of an individual has a lot of influence on his/her well-being & may contribute to aggravation of acne.

In our study, the most frequently consumed food items were chicken products (35.3%). Intake of commercial chicken feed and commercial chicken meat may be the potential cause of development of polycystic ovary syndrome in females due to steroid hormonal imbalance.¹⁹ As seen in other studies, medical students reported increased consumption of fast-food (74.54%), use of cosmetics (32.73%), and decreased intake of water (29.09%) as aggravating and influencing factors for acne.²⁰ Out of those who experience acne, our study showed that half the students consumed less than 5 glasses of water a day.

Acne may lead to complications such as pigmentations and scarring, which accounted for 62.7% and 6% of our study sample whereas the remaining 32.2% developed no complications. The incidence of complications of acne varies across the world. A study from Malaysia showed that 59% developed acne scars,²¹ while a study among medical students in Baghdad reported that pigmentation developed in 30% and scarring developed in 21% participants.²²

CONCLUSION

Our study concludes that many factors are responsible for the development of acne. Of these, frequent use of cosmetics, decreased water intake and large portions of processed and farm chicken in diet are the leading modifiable factors that require attention. Academic stress also turns out to be the most significant cause of acne vulgaris in the medical students.

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REFERENCES

1. Babar O, Mobeen A. Prevalence and Psychological Impact of Acne Vulgaris in Female Undergraduate Medical Students of Rawalpindi and Islamabad, Pakistan. *Cureus* 2019;11:e5722.
2. Abbas MY, Mohammed AZ. Prevalence, clinical types, aggravating factors, and complications of acne vulgaris among medical students in al-Kindy College of Medicine. *Education* 2020;352:313.
3. Ogedegbe EE, Henshaw EB. Severity and impact of acne vulgaris on the quality of life of adolescents in Nigeria. *Clin Cosmet Investig Dermatol* 2014;7:329-34.
4. Sood S, Jafferany M, Vinaya Kumar S. Depression, psychiatric comorbidities, and psychosocial implications associated with acne vulgaris. *J Cosmet Dermatol* 2020;19:3177-82.
5. Fakour Y, Noormohammadpour P, Ameri H, Ehsani AH, Mokhtari L, Khosrovanmehr N. The effect of isotretinoin (roaccutane) therapy on depression and quality of life of patients with severe acne. *Iran J Psych* 2014;9:237-41.
6. Alajlan A, Al Turki YA, AlHazzani Y, Alhowaish N, AlEid N, Alhozaimi Z, et al. Prevalence, level of knowledge and lifestyle association with acne vulgaris among medical students. *J Dermat Surg* 2017;21:58-61.
7. Zhu L, Shen MX, Samran E, Tu YT, Chen X, Tao J, et al. Prevalence of acne in Chinese college students and its associations with social determinants and quality of life: a population-based cross-sectional study. *Chin Med J* 2021;134:1239-41.
8. Tan JK. Psychosocial impact of acne vulgaris: evaluating the evidence. *Skin Therapy Lett* 2004;9:1-9.
9. Green J, Sinclair RD. Perceptions of acne vulgaris in final year medical student written examination answers. *Australas J Dermatol* 2001;42:98-101.
10. Hui RW. Common misconceptions about acne vulgaris: A review of the literature. *Clin Dermat Rev* 2017;1:33-6.
11. Vilar GN, Santos LA, Sobral Filho JF. Quality of life, self-esteem, and psychosocial factors in adolescents with acne vulgaris. *An Bras Dermatol* 2015;90:622-9.
12. El-Hamd MA, Nada EEA, Moustafa MA, Mahboob-Allah RA. Prevalence of acne vulgaris and its impact of the quality of life among secondary school-aged adolescents in Sohag Province, Upper Egypt. *J Cosmet Dermatol* 2017;16:370-73.
13. Abo El-Fetoh NM, Alenezi NG, Alshamari NG, Alenezi OG. Epidemiology of acne vulgaris in adolescent male students in Arar, Kingdom of Saudi Arabia. *J Egypt Public Health Assoc* 2016;91:144-9.
14. Muthupalaniappen L, Tan HC, Puah JW. Acne prevalence, severity and risk factors among medical students in Malaysia. *Clin Ter* 2014;165:187-92.
15. Perić J, Maksimović N, Janković J, Mijović B, Reljić V, Janković S. Prevalence and quality of life in high school pupils with acne in Serbia. *Vojnosanit Pregl* 2013;70:935-9.
16. Yahya H. Acne vulgaris in Nigerian adolescents--prevalence, severity, beliefs, perceptions, and practices. *Int J Dermatol* 2009;48:498-505.
17. Naveed M, Bashir S, Khalid S, Qamar S, Shahid M, Raheela HW. Risk Factors of acne vulgaris among young females. *J Humanit Cult Stud* 2020;958:116-21.
18. Chiu A, Chon SY, Kimball AB. The response of skin disease to stress: changes in the severity of acne vulgaris as affected by examination stress. *Arch Dermatol* 2003;139:897-900.
19. Ahmad S, Ahmed I, Haider S, Batool Z, Ahmed SB. Daily consumption of commercial chicken feed and meat lead to alterations in serum cholesterol and steroidal sex hormones in female rats. *Pak J Pharm Sci* 2017;30:257-61.
20. Sachdeva M, Tan J, Lim J, Kim M, Nadeem I, Bismil R. The prevalence, risk factors, and psychosocial impacts of acne vulgaris in medical students: a literature review. *Int J Dermatol* 2021;60:792-98.
21. Muthupalaniappen L, Tan HC, Puah JW, Apipi M, Sohaimi AE, Mahat NF, et al. Acne prevalence, severity, and risk factors among medical students in Malaysia. *Clin Ter* 2014;165:187-92.
22. Sadiq MA, Salih AA, Jamil NF. Acne among Medical Students in Baghdad, Pattern and Associated Factors. *Int J Family Med Healthcare* 2023;2:1-7.

Dermoscopy assessment of treatment response of scabies patients

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Objective: To assess the use of dermoscopy in managing scabies, highlighting its role in enhancing diagnostic accuracy and treatment efficacy.

Methodology: This cross-sectional study included 60 patients of scabies and was undertaken at the Duhok Dermatology Teaching Center in Duhok city, from May 2023 to October 2023. Dermoscopy was compared with clinical diagnosis. For data analysis, SPSS was utilized.

Results: A strong correlation was discovered between the efficacy of dermoscopy and the evaluation of scabies cases' response to treatment, which was

substantiated by a p-value of 0.0000 and a t-value of 10.225. based on the R-squared value of 0.643, which indicates that dermoscopy may explain approximately 64.3% of the variability in treatment response evaluation.

Conclusion: Dermoscopy significantly enhances the accuracy of scabies diagnosis, providing a reliable, non-invasive tool that complements clinical examination.

Keywords: Dermoscopy, assessment, treatment, scabies, patients.

INTRODUCTION

Scabies, a highly contagious skin condition caused by the human itch mite *Sarcoptes scabiei*, affects approximately 150-200 million people annually, particularly in overcrowded and substandard housing conditions.¹ The primary symptom, intense pruritus, especially at night, significantly disrupts sleep and impacts quality of life. A positive family history is common, highlighting the contagious nature of the disease.²

Diagnosis is typically clinical, based on severe itching and characteristic skin lesions. The 2020 International Alliance for the Control of Scabies (IACS) developed diagnostic standards categorized into Confirmed, Clinical, and Suspected Scabies through a modified Delphi study involving 34 experts. Confirmed Scabies requires direct identification of mites, eggs, or feces via microscopy or high-powered imaging devices such as video-dermoscopy and dermoscopy. Clinical Scabies is diagnosed based on scabies burrows, lesions in typical locations, or typical lesions with historical features. Suspected Scabies is diagnosed based on atypical lesions and historical features.³

On examination, scabies presents with erythematous papules, vesicles, or nodules, commonly located on the interdigital webs, wrists, armpits, genitals, buttocks, groins, and breasts in women.⁴ The burrows can be obscured by eczematous changes, crusting, and scratching, making them difficult to detect with the naked eye.⁵ Transmission occurs through close human contact, both sexual and non-sexual, and less commonly via fomites like clothing or bed linens.⁶

The conventional diagnostic method involves examining scales collected by skin scraping under a microscope to identify mites, eggs, or feces. Due to its low sensitivity, multiple tests are often required for a definitive diagnosis, which can be time-consuming in a busy clinical setting.⁷ Alternative diagnostic methods include the burrow ink test, adhesive tape test, and PCR-based techniques for detecting *S. scabiei* DNA in skin scrapings.⁸

Dermoscopy has emerged as a significant advancement in diagnosing and managing scabies. This non-invasive, real-time observation method allows for improved visualization of skin lesions. Unlike microscopic examination, which involves scraping one or two lesions, dermoscopy can quickly screen multiple lesions, providing a more comprehensive assessment. Dermoscopic images aid in confirming the diagnosis, enhance patient confidence in the treatment regimen, and improve compliance.⁹ The dermoscope's ability to provide detailed images of mites, burrows, and eggs facilitates effective monitoring of treatment response, ensuring that therapeutic protocols are suitable and effective.¹⁰ This study aimed to assess the use of dermoscopy and its role in enhancing diagnostic accuracy and treatment efficacy.

METHODOLOGY

From May 2023 to October 2023, we conducted this descriptive cross-sectional study at the Dermatology Department of Azadi Hospital in Duhok City. The study was approved by Kurdistan Board of Medical Specialties Research Protocol Ethics Committee (Ref No. 21201351

dated May 23, 2023). Verbal consent was obtained from all participants. The study sample consisted of 60 patients of all ages and both gender, each clinically diagnosed with scabies by a dermatologist.

Detailed patient histories were obtained, and comprehensive dermatological examinations were conducted. Dermoscopy, the transillumination of skin lesions with magnification to visualize fine details, relies on the physical properties of the skin that affect the reflection, refraction, diffraction, and absorption of light. The primary types of dermatoscopes include handheld dermatoscopes (HHD), also known as smart dermatoscopes, and video dermatoscopes. We utilized a handheld Derm Lite DL4 dermoscope with 10x magnification power for lesion examination. This dermoscope does not require a liquid interface for application.

During dermoscopic examination, the presence of a mite was suspected upon identifying a triangular structure followed by a burrow (Fig.). Mites and burrows were meticulously documented. To

Table 1: Demographic variables.

Variables		Frequency	%
Age groups (years)	1-10	22	36.7
	11-20	21	35.0
	21-30	8	13.3
	31-40	5	8.3
	41-50	4	6.7
Gender	Females	32	53.3
	Males	28	46.7
Residency	Duhok	44	73.3
	Domiz	5	8.3
	Khanke	4	6.7
	Zakho	7	11.7
Occupation	Employee	9	15.0
	Un-employee	51	85.0
Family members	≤4	12	20.0
	>4	48	80.0
Clinical finding	Burrows	2	3.3
	Excoriations	11	18.3
	Excoriations + burrows	7	11.7
	Excoriations + papules	18	30.0
	Excoriations + papules + burrows	16	26.7
	Papules + nodules	6	10.0
Dermatoscope finding	Burrow + Mites	9	15.0
	burrows	5	8.3
	Burrows + mites	46	76.7
Clinical diagnosis	Positive	31	51.7
	Negative	29	48.3
Dermatocope diagnosis	Positive	31	51.7
	Negative	29	48.3
Total		60	100.0

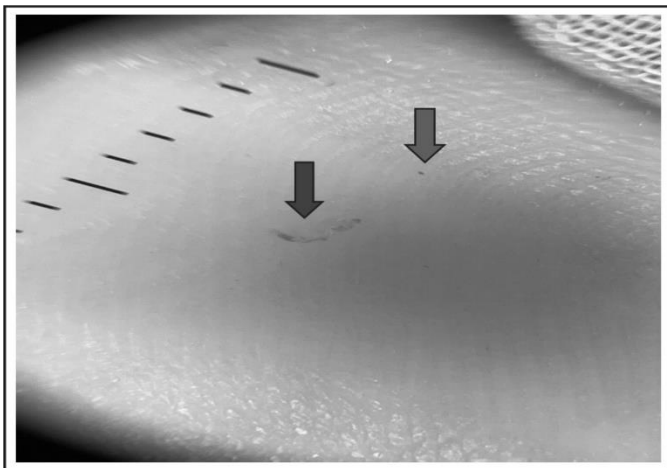


Fig. 1: Dermoscopy showing typical pattern (jet with contrail) at X10 magnification. It consists of the triangular shaped mite (blue arrow), trailed by the burrow (red arrow).

minimize and prevent cross-contamination among patients, the dermoscope lenses were thoroughly cleaned with antiseptic wipes containing bactericidal and alcohol-based gel after each use.

Statistical Analysis: We used SPSS version 22. Associations between categorical variables were assessed using the Chi-square test. Pearson correlation was employed to evaluate the relationship between continuous variables. A p-value of 0.05 or less was considered statistically significant.

RESULTS

Out of 60 patients, 32 were females. Mean age was 17 ± 12 years. We found that 26.7% patients were diagnosed clinically as Excoriations + burrows and Excoriations + papules and 76.7% had Burrows + mites on dermatoscope diagnosis and 51.67% of patients have

positive scabies diagnosis clinically and by dermatoscope (Table 1). There was no significant association between dermatoscope diagnosis of scabies and age groups, gender, residency, occupation or family history (Table 2).

There was significant association between dermatoscopy diagnosis and clinical diagnosis of scabies as, 87.1% of patients diagnosed clinically as scabies infection confirm diagnosed as scabies by dermatoscopy with sensitivity 87.1% and specificity 93.1% (Table 3).

DISCUSSION

The findings from our study provide significant insights into the demographic and clinical characteristics of scabies patients, as well as the effectiveness of dermoscopy in diagnosing scabies. The mean age of our patients was 17 ± 12 years, with a notable prevalence in younger age. This demographic distribution aligns with previous studies indicating that scabies is particularly prevalent among children and adolescents due to their close physical contact and less developed hygiene practices.^{11,12} Gender distribution in our study showed a slight female predominance (53.3% females vs. 46.7% males). This is consistent with a previous study.¹³ A significant proportion of our study population resided in Duhok City (73.3%), and 85% were unemployed. Additionally, 80% of patients had family sizes exceeding four members. These findings underscore the association between scabies and socioeconomic factors such as overcrowding and unemployment, which are well-documented risk factors for the transmission of scabies.¹⁴

Clinically, 30% of patients were diagnosed with excoriations plus burrows, and 26.7% with excoriations plus papules. Dermoscopic examination revealed that 76.7% of patients had burrows and mites. Previous studies have

Table 2: Association between dermatoscopic diagnosis and study variables.

Variables		Dermatoscopy		p-value
		Negative	Positive	
Age Groups (years)	1-10	14 45.2%	8 27.6%	0.6
	11-20	10 32.3%	11 37.9%	
	21-30	4 12.9%	4 13.8%	
	31-40	2 6.5%	3 10.3%	
	41-50	1 3.2%	3 10.3%	
Gender	Females	17 54.8%	15 51.7%	1.000
	Males	14 45.2%	14 48.3%	
Residency	Duhok	20 64.5%	24 82.8%	0.4
	Domiz	4 12.9%	1 3.4%	
	Khanke	3 9.7%	1 3.4%	
	Zakho	4 12.9%	3 10.3%	
Occupation	Employee	3 9.7%	6 20.7%	0.3
	Unemployed	28 90.3%	23 79.3%	
Family Members	≤4	6 19.4%	6 20.7%	1.000
	>4	25 80.6%	23 79.3%	
Total		31 (100%)	29 (100%)	

$p \leq 0.05$ (significant).

Table 3: Association between dermatoscopy diagnosis and clinical diagnosis of scabies.

Variables		Clinical diagnosis		p-value
		Negative	Positive	
Dermatoscopy Diagnosis	Negative	27 93.1%	4 12.9%	0.0001
	Positive	2 6.9%	27 87.1%	
Total		31 (100%)	29 (100%)	

highlighted the value of dermoscopy in enhancing the diagnostic accuracy of scabies by allowing direct

visualization of mites and burrows.¹⁵ Interestingly, 51.67% of patients had a positive scabies diagnosis both clinically and through dermoscopy, indicating a high concordance between these diagnostic methods. This result supports the notion that while clinical diagnosis remains crucial, dermoscopy provides an additional layer of accuracy and confirmation, particularly in ambiguous cases.¹⁶

Our statistical analysis did not find significant associations between dermoscopic diagnosis of scabies and variables such as age group, gender, residency, occupation, and family size. This suggests that dermoscopy's diagnostic accuracy is not influenced by these demographic factors. Notably, we found a significant association between clinical and dermoscopic diagnoses of scabies. Specifically, 87.1% of patients diagnosed clinically with scabies were confirmed through dermoscopy, demonstrating high sensitivity (87.1%) and specificity (93.1%) for dermoscopic diagnosis. This finding aligns with existing literature that underscores dermoscopy's role in confirming clinical diagnoses and reducing false positives and negatives.¹⁷

The high sensitivity and specificity of dermoscopy in our study are corroborated by other studies. Nie et al, demonstrated that dermoscopy had a sensitivity of 91% and a specificity of 86%, further validating our results.¹⁸ The use of dermoscopy not only aids in accurate diagnosis but also enhances patient compliance and satisfaction by providing visual confirmation of the presence of mites and burrows.¹⁸

The study's limited sample size and homogeneity restrict the generalizability of the findings to broader populations or specific demographics. The lack of comparison with other commonly used diagnostic techniques for scabies limits the assessment of dermoscopy's relative effectiveness. The study utilized a single treatment regimen, which does not account for potential resistance or non-compliance issues that might affect treatment outcomes.

CONCLUSION

Dermoscopy significantly enhances the accuracy of scabies diagnosis, providing a reliable, non-invasive tool that complements clinical examination. This can improve patient outcomes by ensuring accurate identification and appropriate treatment of scabies, ultimately optimizing healthcare resources and reducing misdiagnosis.

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REFERENCES

1. Akuta T, Minegishi D, Kido N, Imaizumi K, Nakaoka S, Tachibana SI, et al. Development of a rapid scabies immunodiagnostic assay based on transcriptomic analysis of *Sarcoptes scabiei* var. *nyctereutis*. *Sci Rep* 2021;11:6455-8.
2. Ständer S, Ständer S. Itch in Scabies-What Do We Know? *Front Med (Lausanne)*. 2021;8:628392.
3. Engelman D, Yoshizumi J, Hay RJ. The 2020 International Alliance for the Control of Scabies Consensus Criteria for the Diagnosis of Scabies. *Br J Dermatol* 2020;183:808-20.
4. Furuya K, Nakajima H, Sasaki Y, Ishiko A, Urita Y. A scabies outbreak in a diabetic and collagen disease ward: Management and prevention. *Exp Ther Med* 2016;12:3711-5.
5. Nie YL, Yi H, Xie XY, Fu GL, Zheng YQ. Dermoscopic features of children scabies. *Front Med (Lausanne)* 2023;10:1097999.
6. Murray RL, Crane JS. Scabies. [Updated 2023 Jul 31]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK544306/>
7. Kosmala A, Kowalczyk MJ, Żaba R. Dermoscopy, light microscopy, and real-time polymerase chain reaction for the diagnosis of scabies. Preliminary results. *Postepy Dermatol Alergol* 2021;38:578-584.
8. Micali G, Lacarrubba F, Verzi AE, Chosidow O, Schwartz RA. Scabies: Advances in Noninvasive Diagnosis. *PLoS Negl Trop Dis* 2016;10(6):e0004691.
9. Sonthalia S, Agrawal M, Bhatia J. Entodermoscopy Update: A Contemporary Review on Dermoscopy of Cutaneous Infections and Infestations. *Indian Dermatol Online J* 2021;12:220-236.
10. Li FZ, Chen S. Diagnostic Accuracy of Dermoscopy for Scabies. *Korean J Parasitol* 2020;58:669-74.
11. Gunning K, Kiraly B, Pippitt K. Lice and Scabies: Treatment Update. *Am Fam Physician* 2019;99:635-642.
12. Welch E, Romani L, Whitfeld MJ. Recent advances in understanding and treating scabies. *Fac Rev* 2021;10:28-32.

13. Khalil S, Abbas O, Kibbi AG, Kurban M. Scabies in the age of increasing drug resistance. *PLoS Negl Trop Dis* 2017;11(11):e0005920.
14. Thean LJ, Engelman D, Kaldor J, Steer AC. Scabies: New Opportunities for Management and Population Control. *Pediatr Infect Dis J* 2019;38:211-3.
15. Lallas A, Giacomel J, Argenziano G. Dermoscopy in general dermatology: practical tips for the clinician. *Br J Dermatol* 2014;170:514-26.
16. Abdel-Latif AA, Elshahed AR, Salama OA, Elsaie ML. Comparing the diagnostic properties of skin scraping, adhesive tape, and dermoscopy in diagnosing scabies. *Acta Dermatovenerol Alp Pannonica Adriat* 2018;27:75-8.
17. Gürel MS, Turgut Erdemir AV, Tekin B. A Case Report of Real-Time in vivo Demonstration of *Sarcoptes scabiei*. *Türkiye Parazitol Derg* 2017;41:229-232.
18. Nie YL, Yi H, Xie XY, Fu GL, Zheng YQ. Dermoscopic features of children scabies. *Front Med (Lausanne)* 2023;10:1097999.

Role of different therapeutic systems to reduce the risk of cardiovascular complications by intervening type II diabetes

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Objective: To assess the risk-reduction of cardiovascular complications in patients of type-II diabetes through standardized tools of evidenced-based-medicine.

Methodology: This cross-sectional observational study was conducted at outpatient care-centers. The study included 200 patients and duration was July-2019 to June-2020. For the treatment of type-II diabetes, patients have taken either allopathic, herbal, homeopathic and/or combination systems of medicine. Endpoints of study were any cardiovascular-outcome; myocardial-infarction, hypertension, angina-pectoris, heart-failure, stroke, thrombo-embolism, coronary-artery disease, cardiac-arrhythmia.

Results: Relative-risk-reduction (RRR) of cardiovascular complications as per treatment duration <1 years allopathic system v/s homoeopathic: 62.12%, Number-Needed-to-Treat (NNT)≈5.0; RRR in 5.10-7.0 years allopathic system v/s herbal: 54%, NNT≈2.0; RRR in 7.10-10.0 years allopathic system v/s herbal:

30%, NNT≈7.0; allopathic-system v/s combination: 50%, NNT≈3.0; RRR in 10.10-15.0 years allopathic-system v/s combination: 24%, NNT≈8.0; RRR in 15.10-20.0 years allopathic-system v/s combination: 16%, NNT≈6.0; RRR in 20.10-25.0 years allopathic-system v/s combination: 67%, NNT≈2.0. Patients took diet of low-calorie; RRR by allopathic-system v/s combination: 1.25%, NNT≈222. In combination systems; RRR by allopathic herbal system v/s allopathic homoeopathic: 49.36%, NNT≈7.

Conclusion: In short-term treatment (<5 years), risk reduction of cardiovascular complications was better with alternative medicines compared to allopathic system. However, in long-term treatment (>5 years), risk-reduction of cardiovascular complications was better in allopathic-system compared to alternative system of medicine.

Keywords: Cardiovascular; chronic complications, diabetes mellitus, number-needed-to-treat, relative-risk-reduction.

INTRODUCTION

Chronic hyperglycemia is the main predictor of macrovascular complications in patients of type-II diabetes (T2D).¹ In T2D, endogenous ET-1 (Endothelin-1) is enhanced on ETA (Endothelin A) receptors, which is responsible for vasoconstriction.² This abnormality may participate in the pathophysiology of vascular complications associated with T2D.³

Strategies to prevent microvascular complications are improving glycemic control, aggressive treatment of risk factors for coronary heart disease and the primary prevention of non-alcoholic diuretic drug-induced hypoglycemia.⁴ Atherosclerosis in macro-vascular regions lead to arterial necrosis and ultimately narrowing of arteries.⁵

Another evidence mentioned that due to inflammation and damage of endothelial cells of arteries, oxidized LDL (Low Density Lipo-protein) deposits in the endothelial layers.⁶ This process of damage starts from the angiotensin II (A-II) activation. Afterwards; monocytes

distribute as a phagocytic cells once they are penetrated into the walls of arteries, form froth cells. Froth cells promote the production of T-lymphocyte macrophages. Ultimately; a lipid rich atherogenic cyst produced; the death of vessels occurs due to rupture of this cyst.⁷

T2D patients have enhanced adhesion of platelet due to transformed calcium control, hypercoagulability, lower formation of nitric oxide and higher formation of free radicals.⁸ The vascular obstruction and cardiovascular complications (CVC) in T2D are due to elevated coagulability and compromised fibrinolysis.⁹ Plenty of high quality evidences are available; however; clear description of mechanisms are not available through which diabetes increases the threat of atherosclerotic development and death.¹⁰

Studies pertaining to alternative and complementary medicine (ACM) are now a day's a focus of clinicians. Globally, many individuals rely on ACM for the treatment of their health disorders.¹¹ Almost 50% of Pakistani population prefers ACM for different ailments;

common choices of population are herbal remedies, homeopathy or combination therapies.¹² Based upon these criteria, assessment of risk-reduction of cardiovascular complications in patients of type-II diabetes was the main goal of study. Assessment was done by standardized tools of evidenced-based-medicine.

METHODOLOGY

This observational cross-sectional is a part of a large study conducted in outpatient clinics in the city of Karachi on T2D patients from July-2019 to June-2020. Two hundred patients were enrolled having T2D. The treatment arms of study were herbal, allopathic, homeopathic and/or combination (Fig. 1). Primary endpoints of study were any cardiovascular outcome; hypertension, angina pectoris, myocardial infarction, heart failure, stroke, thrombo-embolism, coronary artery disease, cardiac arrhythmia. The study was approved by Institutional Bioethics Committee, University of Karachi (Project No. IBC KU 23), and advanced Studies and Research Board, University of Karachi (Reference No. ASRB/03274/Pharm). A written informed consent was obtained from each patient.

A total of 196 T2D patients should be enrolled in the study; this minimum size of sample was determined by precision analysis technique.¹³ Patients had the confirmed diagnosis of T2D, complete records of the fasting blood sugar (FBS), random blood sugar (RBS) and glycated hemoglobin (HbA1c). Juvenile and type 1 diabetic patients, gestational diabetic patients, latent autoimmune diabetes in adults (LADA) patients were excluded from the study.

A questionnaire was designed to collect data. All researchers ensured patient's data confidentiality in compliance with the Declaration of Helsinki.¹⁴ Questionnaires were filled by health practitioners in the

specialty of pharmacy, family medicine, homeopathy and hikmat (herbal practitioners). Analysis of data was done by determining relative risk, RRR, absolute risk reduction (ARR) of any CVC and NNT; these tools are standardized by Evidence Based Medical (EBM) practice for comparative evaluation of different drugs or therapeutic systems.¹⁵ RRR is the difference in event rates in the form of proportion; it compares two treatment groups.¹⁶ The NNT refers that how many patients should be treated to get the experience of desire outcome in one patient.¹⁷

Statistical Analysis: The data analysis was performed by SPSS version 22.

RESULTS

Out of 200 patients, 103 (51.7%) were male and 97 (48.3%) females. Mean age of male was 54 years and females, 52 years.

End points of study were RRR, ARR of cardiovascular complications and NNT analysis for reduction of one cardiovascular complication. RRR, ARR and NNT were compared in between systems of medicine with duration of treatments (Table 1). In between treatment type and insulin status, in between treatment type and physical activity, in between treatment type and diet status (Table 2) and in between treatment types (Table 3).

DISCUSSION

Diabetes affects more than one hundred eighty (>180) million individuals around the world.¹⁸ Cardiovascular morbidity and mortality are closely associated with diabetes and insulin resistance.¹⁹ In current outcomes research, to determine RRR, ARR and NNT, allopathic system of treatment was considered as standard. The main reason for choosing allopathic system as standard is preference of most of the patients (47%).

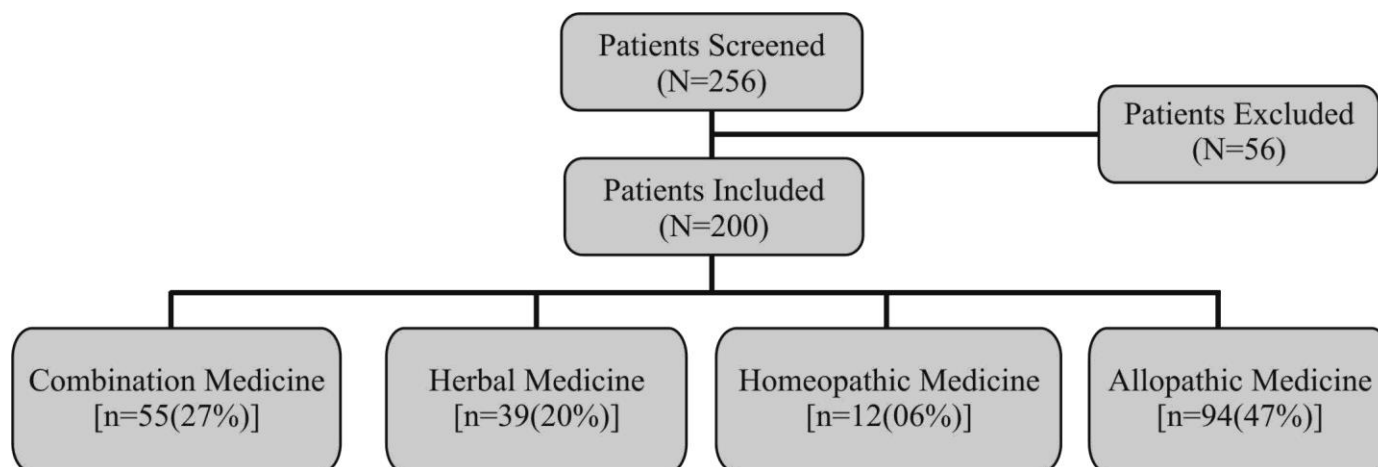


Fig. 1: Therapeutic arms of different treatments.

Table 1: Relative Risk, RRR^a, ARR^b and NNT^c for one cardiovascular outcome with duration.

Duration of Treatment (Years)	Any Cardiovascular Complication in treatment				Relative Risk	RRR ^a	ARR ^b	NNT ^c
	Allopathic	Homeopathic	Herbal	Combination				
< 1	12.50%	33%	-----	-----	0.38	62.12%	20.50%	4.87 ≈ 5.0
		-----	9%	-----	3.33	-233%	-3.50%	-28.57 ≈ -29.0
		-----	-----	12.50%	0	0%	0%	-----
1.1 to 3.5	30%	17%	-----	-----	1.76	-76.47%	-13%	-7.69 ≈ -8.0
		-----	6.25%	-----	4.80	-380%	-23.75%	-4.21 ≈ -4.0
		-----	-----	12.50%	2.40	-140%	-17.50%	-5.71 ≈ -6.0
3.6 to 5.0	23%	50%	-----	-----	1.54	-54%	27%	-3.70 ≈ -4.0
		-----	15%	-----	1.53	-53%	-8.0%	-12.50 ≈ -13.0
		-----	-----	12%	1.92	-92%	-11%	-9.09 ≈ -9.0
5.1 to 7.0	46%	4%	-----	-----	11.50	-1050%	-42%	-2.38 ≈ -2.0
		-----	99%	-----	0.46	54%	53%	1.88 ≈ 2.0
		-----	-----	25%	1.84	-84%	-21%	-4.76 ≈ -5.0
7.1 to 10	35%	-----	50%	-----	0.70	30%	15%	6.66 ≈ 7.0
		-----	-----	70%	0.50	50%	35%	2.85 ≈ 3.0
10.1 to 15	38%	-----	-----	50%	0.76	24%	12%	8.33 ≈ 8.0
15.1 to 20	83%	-----	-----	99%	0.84	16%	16%	6.25 ≈ 6.0
20.1 to 25	33%	-----	-----	99%	0.33	67%	66%	1.51 ≈ 2.0

^aRelative Risk Reduction; ^bAbsolute Risk Reduction; ^cNumber Needed to Treat**Table 2: Relative Risk, RRR^a, ARR^b and NNT^c for one cardiovascular outcome and insulin use status, exercise status and low-calorie diet status.**

	Any Cardiovascular Complication in treatments				Relative Risk	RRR ^a	ARR ^b	NNT ^c
		Allopathic	Herbal	Combination				
Insulin Status	With Insulin	37%	-----	31%	1.19	-19.35%	-6.0%	-16.66 ≈ -17.0
	Without Insulin	31%	5.12%	-----	6.05	-505.46%	-25.88%	-3.86 ≈ -4.0
			-----	21.42%	1.44	-44.72%	-9.58%	-10.43 ≈ -10.0
Exercise & Physical Activity Status	Exercise	31.25%	11.11%	-----	2.81	-181.27%	-20.14%	-4.96 ≈ -5.0
			-----	30%	1.04	-4.16%	-1.25%	-80.0
	Without Exercise	35.44%	3.33%	-----	10.64	-964.26%	-32.11%	-3.11 ≈ -3.0
			-----	22.22%	1.59	-59.49%	13.22%	-7.56 ≈ -8.0
Low Caloric Diet Status	Low Caloric Diet	35.55%	9.52%	-----	3.73	-273%	-26.03%	-3.84 ≈ -4.0
			-----	36%	0.98	1.25%	0.45%	222.22 ≈ 222
	Without Low Caloric Diet	34%	-----	13.33%	2.55	-155%	-20.67%	-4.83 ≈ -5.0

^aRelative Risk Reduction; ^bAbsolute Risk Reduction; ^cNumber Needed to Treat

In less than 1.00 year of treatment; RRR of any CVC was 62.12% with allopathic treatment versus homoeopathic treatment and in every 05 patients on the treatment of allopathic system; one patient (NNT $\approx$ 5) will not have any CVC compared to homoeopathic system. In comparison to herbal system, RRR of any CVC was -233% while negative results of NNT shows increased risk of any CVC and compare to herbal system NNT $\approx$ -29.

Hence in less than one-year treatment; allopathic system of medicine is better than homoeopathic system while herbal system is better than allopathic system. If the duration of treatment is more and in between 1.10 years to 3.50 years; incidences of any CVC with allopathic system were high (30%) compared to homoeopathic (17%), herbal (6.25%) and combination (12.50%) systems. Hence RRR for any CVC with allopathic system is -76.47%, -380% and -140% compared to homoeopathic, herbal and combination systems respectively. NNT analysis also favors the homoeopathic system (NNT $\approx$ -8), herbal system (NNT $\approx$ -4) and combinations (NNT $\approx$ -6) systems.

Similarly, RRR of any CVC and NNT to reduce one CVC were not in the favor of allopathic system for the duration of 3.60 years to 5.00 years; RRR (allopathic compared to homeopathic -54%) and NNT $\approx$ -4.0; RRR (allopathic compared to herbal -53%) and NNT $\approx$ -13.0; RRR (allopathic compared to combination -92%) and NNT $\approx$ -9.0. In contrast, risk reduction of CVC by allopathic system of treatment was better compared to other systems in between 5.10 to 7.0 years follow-up; where RRR (allopathic compared to herbal 54%) and NNT $\approx$ -2.0; for the duration of 7.10 to 10.0 years RRR (allopathic compared to herbal 30%) and NNT $\approx$ -7.0, while RRR (allopathic compared to combination 50%) and NNT $\approx$ 3.0. From 10.10 years to 25.00 years follow-up allopathic system was only compared with combination system of treatment.

Such long-term data was only available with these two systems of medicine. The comparison of allopathic with combination system revealed all results in the favor of allopathic system and RRR and NNT by allopathic treatment were 24% and $\approx$ 8.0 respectively (10.10 to 15.0 years); RRR and NNT by allopathic treatment were 16% and $\approx$ 6.0 respectively (15.10 to 20.0 years); RRR and NNT by allopathic treatment were 67% and $\approx$ 2.0 respectively (20.10 to 25.0 years).

ARR were also calculated, however, due to its little

Table 3: Relative Risk, RRR^a, ARR^b and NNT^c for one cardiovascular outcome and combination therapy.

Any Cardiovascular Complication in treatments		Relative Risk	RRR ^a	ARR ^b	NNT ^c
Allopathic & Herbal	Allopathic & Homoeopathic				
14.28%	28.20%	0.506	49.36%	13.92%	7.18 $\approx$ 7.0

^aRelative Risk Reduction; ^bAbsolute Risk Reduction; ^cNumber Needed to Treat

clinical significance, they cannot be used for interpretation of results rather they are important for NNT calculations.¹⁷ In 5.10 to 7.0 years follow-up; homoeopathic system and combination system were better compare to allopathic system in terms of RRR and NNT analysis; RRR (allopathic compare to homeopathic -1050%) and NNT $\approx$ -2.0, while allopathic system versus combination system RRR and NNT were -84% and $\approx$ -5.0 respectively (Table 1).

Findings of the study were also evaluated for CVC reduction in between those patients getting Insulin and those who were not getting Insulin; while these patients were taking oral treatment of T2D either by allopathic, herbal or combination system of medicine. In the group of patients who were taking Insulin; RRR of CVC by allopathic system of medicine was -19.35% and NNT $\approx$ -17.0 compared to combination system of medicine.

It seems that if a patient is taking Insulin, outcomes of combination treatments are better compared to allopathic treatments. Findings on those patients who were not taking Insulin were not different; RRR of CVC by allopathic system were -504.46% and NNT $\approx$ -4.0 compared to herbal system; RRR of CVC by allopathic system were -44.72% and NNT $\approx$ -10.0 compared to combination system of medicine. However, these contrary findings are regardless of duration of treatment (Table 2).

Unfortunately; very little literature is available to compare quantitative data regarding risk reduction of CVC by homoeopathic, herbal and combination system of medicine. Most of the published evidence is for the allopathic system. Piepoli et al, mentioned in their study that allopathic medicines (Lipid Lowering Agents) reduced the risk of cardiovascular disease (CVD) and myocardial infarction (MI) by 20 -25%.²⁰ Empagliflozine, a new anti-diabetic medication have shown in recent trials significant reduction of heart failure by 35%, CVD related death by 28% and all-cause mortality by 32%.²¹

Interestingly, in exercise group and non-exercise group, when all these therapeutic systems were evaluated; CVC

risk reduction and NNT were not in favor of allopathic system in both exercise and non-exercise groups (Table 2). Risk reduction of CVC was also determined with and without low caloric diet of T2D patients. In patients taking diet with low calorie, RRR (allopathic compared to herbal -273%) and NNT $\approx$ -4.0 for CVC; while RRR (allopathic compared to combination 1.25%) and NNT $\approx$ 222.

These results in patients taking low caloric diet clearly indicated that allopathic system is better than combination system in reducing the risks of CVC, while compared to herbal system, allopathic system did not show better outcomes. Similarly, in patients without low caloric diet, RRR (-155%) and NNT ($\approx$ -5.0) were in the favor of combination system of medicine rather than allopathic system. (Table – 2) In allopathic treatment; anti-platelet therapy by low dose aspirin reduces the risk of CVC in diabetic patients by more than 10%.²²

In combination system of medicine two different combinations were used. These combinations were allopathic+herbal systems and allopathic+homoeopathic system. (Table – 3). RRR of CVC (allopathic+herbal compared to allopathic+homoeopathic 49.36%) and NNT $\approx$ 7.0. These findings indicate that allopathic+herbal combination is superior compared to allopathic+homoeopathic combination.

Current study is unique in a sense that it is conducted first time in Pakistan, where systems of treatment were compared based upon EBM criteria of measures. Unfortunately, globally very limited data is available for such direct comparison of different therapeutic systems; due to such limitation, data for comparison of findings are not available frequently. Despite all these facts, in cross sectional study the researcher mostly interacts only once with the study population, so it is not possible to exactly determine the effect of any treatment system (Allopathic or alternative) for Type II DM on CV end points. To scientifically determine the impact of any treatment system for Type II DM, on CV end points is to conduct a prospective randomized trial on different treatment modalities for Type II DM. Therefore, current study is just providing an idea of CV endpoints for conduct of large randomized clinical trials.

CONCLUSION

In short term treatment (<5 years); risk reduction of CVC was better with ACM in comparison to allopathic treatment in T2D. However, in long term treatment (>5 years); outcomes of current study clearly indicated that allopathic treatment is better than ACM for risk reduction of CVC. In combination medicine, the allopathic herbal system of medicine is superior compared to allopathic

homoeopathic system in reducing the risk of CVC in T2D patients.

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REFERENCES

- Cardoso C, Leite N, Moram C, Salles G. Long-term visit-to-visit glycemic variability as predictor of micro- and macrovascular complications in patients with type 2 diabetes: the Rio de Janeiro Type 2 Diabetes Cohort Study. *Cardiovasc Diabetol* 2018;17:1-16.
- Kostov K. The causal relationship between endothelin-1 and hypertension: Focusing on endothelial dysfunction, arterial stiffness, vascular remodeling, and blood pressure regulation. *Life* 2021;11:01-16.
- Schalkwijk C, Stehouwer C. Methylglyoxal, a highly reactive dicarbonyl compound, in diabetes, its vascular complications, and other age-related diseases. *Physiol Rev* 2020;100:407-61.
- Jenkins AJ, Scott E, Fulcher J, Kilov G, Januszewski AS. Management of diabetes mellitus. In: Toth P, Cannon C, editors. *Comprehensive Cardiovascular Medicine in the Primary Care Setting*: Humana Press, Cham; 2019. p. 113-77.
- Paul S, Ali A, Katare R. Molecular complexities underlying the vascular complications of diabetes mellitus—A comprehensive review. *JDC* 2020;34:107613-24.
- Itabe H, Kato R, Sawada N, Obama T, Yamamoto M. The significance of oxidized low-density lipoprotein in body fluids as a marker related to diseased conditions. *Curr Med Chem* 2019;26:1576-93.
- Robinson NA, Loynachan AT. Cardiovascular and hematopoietic systems. In: Zimmerman JJ, Karriker LA, Ramirez A, Schwartz KJ, Stevenson GW, Zhang J, editors. *Diseases of swine*. 11th ed. Pondicherry, India: John Wiley & Sons, Inc.; 2019. p. 221-33.
- Farah C, Michel LY, Balligand J-L. Nitric oxide signalling in cardiovascular health and disease. *Nat Rev Cardiol* 2018;15:292-316.
- Patel TP, Rawal K, Bagchi AK, Akolkar G, Bernardes N, Dias DD, et al. Insulin resistance: an additional risk factor in the pathogenesis of cardiovascular disease in type 2 diabetes. *Heart Fail Rev* 2016;21:11-23.
- Gnatiuc L, Herrington WG, Halsey J, Tuomilehto J, Fang X, Kim HC, et al. Sex-specific relevance of diabetes to

- occlusive vascular and other mortality: a collaborative meta-analysis of individual data from 980 793 adults from 68 prospective studies. *Lancet Diabet Endocrinol* 2018;6:538-46.
11. Sen S, Chakraborty R. Revival, modernization and integration of Indian traditional herbal medicine in clinical practice: Importance, challenges and future. *J Tradit Complement Med* 2017;7:234-44.
12. Bukhsh A, Gan SH, Goh B-H, Khan TM. Complementary and alternative medicine practices among type 2 diabetes patients in Pakistan: A qualitative insight. *Eur J Integr Med* 2018;23:43-9.
13. Aparasu RR. Sample Size and Power Analysis; Chapter 13. *Principles of Research Design and Drug Literature Evaluation*. 1. Second ed. United States: Pharmaceutical Press; 2020. p. 139 - 50.
14. Shrestha B, Dunn L. The Declaration of Helsinki on Medical Research involving Human Subjects: A Review of Seventh Revision. *J Nepal Health Res Counc* 2019;17:548-52.
15. Kim DH, Uno H, Wei L-J. Restricted mean survival time as a measure to interpret clinical trial results. *JAMA Cardiol* 2017;2:1179-80.
16. Barratt A, Wyer PC, Hatala R, *et al*. Tips for learners of evidence-based medicine: 1. Relative risk reduction, absolute risk reduction and number needed to treat. *CMAJ* 2004;171:353-8.
17. Aparasu RR, Allison B, Dowling TC. Randomized-Controlled Trials; Chapter 04. In: Aparasu RR, editor. *Principles of Research Design and Drug Literature Evaluation*. 1. Second ed. United States: Pharma. Press; 2020. p. 33 - 44.
18. Zhou B, Lu Y, Hajifathalian K, Bentham J, Di Cesare M, Danaei G, *et al*. Worldwide trends in diabetes since 1980: a pooled analysis of 751 population-based studies with 4·4 million participants. *Lancet* 2016;387:1513-30.
19. Scherer PE, Hill JA. Obesity, diabetes, and cardiovascular diseases: a compendium. *AHA*; 2016. p. 1703-5.
20. Members TF, Piepoli MF, Hoes A.. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts): Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *EJPC* 2016;23:NP1-NP96.
21. Zinman B, Wanner C, Lachin JM. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *NEJM* 2015;373:2117-28.
22. Halvorsen S, Andreotti F, ten Berg JM, Cattaneo M, Coccheri S, Marchioli R, *et al*. Aspirin therapy in primary cardiovascular disease prevention: a position paper of the European Society of Cardiology working group on thrombosis. *J Am Coll Cardiol* 2014;64:319-27.

Cognitive impairment in patients with chronic obstructive pulmonary disease

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Objective: To determine prevalence of mild to severe cognitive impairment in patients with chronic obstructive pulmonary disease (COPD).

Methodology: This hospital-based cross-sectional study was carried out at a pulmonology clinic FRPMC from May to November 2023. It included 67 patients of COPD, age 25 to 65 years. Patient's demographic data was recorded and COPD grouping was done by using ABE assessment tool, which includes GOLD and modified medical research council grades. Cognitive impairment was screened via MOCA scale.

Results: Out of 67 patients 12 were female and rest were male. Average age was 49±10 year. Patients with higher age group, illiterate or previous exposure to coal

or wood had cognitive impairment. We found that 25 patients had normal cognition whereas 22 (32.84%) had mild, 16 (23.88%) moderate and 4 (5.97%) had severe impairment. Most patients having COPD Group E had mild to severe cognitive impairment.

Conclusion: Cognitive impairment was associated with COPD, especially in patients with higher age and moderate to severe disease according to GOLD grades and patient with exacerbation of COPD. Early detection of cognitive impairment is important because it may have physical, social and psychomotor consequences.

Keywords: Cognitive impairment, COPD, Montreal cognitive assessment.

INTRODUCTION

In chronic obstructive pulmonary disease (COPD) focus is on the respiratory health issues of a patient but the declining cognitive function is really ignored. Cognitive impairment is present in up to 60% of people with COPD, with changes in executive function, memory and attention and impacts on crucial outcomes like quality of life, hospitalization, and survival.¹ The prevalence of these impairments is still uncertain, due to non-optimal screening methods.²

Cognitive impairment in COPD patients does not significantly differ by sex, region, educational level, smoking status, or alcohol drinking and its mechanism remains to be uncertain. It seems to be associated with hypoxia-induced neurological damage.³ Hypoxia can impair several cognitive domains such as attention, learning and memory, procession speed and other functions, which are similar in acute and chronic hypoxia. The severity of cognitive deficit correlates with the duration and degree of hypoxia. Brain structural changes with hippocampus and cortex atrophy, ventricle enlargement, senile plaque and neurofibrillary tangle deposition have been observed under chronic hypoxia rather than acute hypoxia.^{4,5}

COPD is associated with progressive decrements in strength and mobility, leading to functional limitations and is often complicated by comorbidities, which further exacerbate functional limitations.⁶ Cognitive impairment

can be assessed by different tools, for example Rapid screening tool (RCT), Mini mental state examination (MMSE) and Montreal cognitive assessment (MOCA). MOCA is superior in assessment of cognitive issues. Post exacerbations pulmonary rehabilitation improves cognitive impairment as evidenced by MOCA scale.^{7,8} The aim of this study was to determine prevalence of cognitive impairment in patients with COPD.

METHODOLOGY

This descriptive cross-sectional study was conducted in the pulmonology outpatient department at Fazaia Ruth Pfau Medical College from May to November 2023. The study was approved by IRB of FRPMC and all participants gave an informed consent. Patients with COPD were included in study. We selected participants using a non-probability consecutive sampling method, specifically targeting those aged 25 to 65. WE excluded individuals with a history of stroke, known causes of dementia, and those admitted within a week following the outpatient department visit.

Detailed histories were taken including hazardous exposures, occupation, addiction and co morbidities. Patients' weight and height were measured. Spirometry was done and patients were classified in GOLD grades according to their FEV1. Patient functional status was assessed according to modified medical research council (mMRC) grade and history of exacerbation taken, then

patients were classified in COPD groups A, B and E using ABE assessment tool.^{9,10}

We conducted a comprehensive evaluation of cognitive function using the Montreal Cognitive Assessment (MoCA).¹¹ This in-depth cognitive appraisal allowed us to categorize participants into different levels of cognitive impairment; mild, moderate, or severe-based on MoCA scores. We traced participants' smoking histories, labeling those who had successfully quit for at least 6 months as "ex-smokers."

Statistical Analysis: Data were analyzed using SPSS version 26. $p < 0.05$ was considered significant.

RESULTS

Out of 67 patients, 55 (82.09%) were males and 12 (17.91%) females (Table 1). Advance age was associated with cognitive impairment significantly ($p = 0.001$). Most patients with cognitive impairment belonged to lower to middle income groups. Also, illiteracy was associated with cognitive impairment (Table 2).

Table 1: Socio-demographic & other variables.

Variable	Number	%
Gender:		
Male	55	82.09%
Female	12	17.91%
Age:		
Male	49.04±10.55	
Female	53.67±10.11	
Age Slabs:		
25 to 34 years	5	7.46%
35 to 44 years	12	17.91%
45 to 54 years	20	29.85%
55 to 64 years	28	41.79%
65 years & Over	2	2.99%
Addiction:		
Smoking	49	73.13%
No Smoking	18	26.87%
Exposure:		
Coal/Wood Cooking	23	34.33%
Chemical fuel	3	4.48%
Aviation fuel	2	2.99%
No Exposure	39	58.21%
Socioeconomic Status:		
Lower	16	23.88%
Middle	36	53.73%
Upper	15	22.39%
Education Level:		
Illiterate	22	32.84%
Primary	2	2.99%
Secondary	6	8.96%

Higher Secondary	12	17.91%
Higher	25	37.31%
Comorbid:		
Asthma	2	2.99%
Diabetes mellitus	6	8.96%
Diabetes mellitus, Hypertension	4	5.97%
Hypertension	12	17.91%
No comorbid	43	64.18%
Categories under calculated BMI:		
Underweight (< 18.5)	2	2.99%
Normal Weight (18.5 to 24.9)	43	64.18%
Overweight (25 to 29.9)	14	20.90%
Obese (≥ 30)	8	11.94%
COPD Grading:		
Mild	13	19.40%
Moderate	20	29.85%
Severe	34	50.75%
Cognitive Impairment:		
Normal	25	37.31%
Mild	22	32.84%
Moderate	16	23.88%
Severe	4	5.97%

While analyzing Gold grades, majority of patients with moderate grades had mild cognitive impairment ($n = 16$, 33.9%) while patients in severe grades having moderate cognitive impairment ($n = 12$, 17.9%). While analyzing COPD groups, patients classified in group E having mild to moderate cognitive impairment ($n = 16$, 23.9%, $n = 12$, 17.9%) respectively (Table 3).

DISCUSSION

The sociodemographic variables in COPD, such as age, education level, and socioeconomic status, have been found to be associated with cognitive impairment in COPD patients.^{12,13} Our results are similar. These sociodemographic variables can serve as important indicators for healthcare providers to identify individuals who may be at a higher risk for cognitive impairment. Age is not only a standalone factor but also interacts with education level and socioeconomic status to influence cognitive function.

Cognitive impairment in COPD patients may not be solely attributed to sociodemographic variables. There are multiple factors that could contribute to cognitive impairment in these patients, including smoking history,

comorbidities, and medication use. Studies have shown that cognitive impairment is more prevalent in patients with COPD who have been exposed to environmental irritants like coal and wood smoke ($=0.002$, $p=0.046$), respectively.^{14,15} Cognitive impairment can impact a patient's ability to effectively manage their COPD, including following treatment plans, recognizing symptoms, and seeking appropriate care. Collaborative care involving healthcare providers, caregivers, and support services is essential for managing COPD in patients with cognitive impairment.¹⁶ By addressing cognitive impairment in COPD patients, healthcare providers can improve overall patient care and quality of life.¹⁷ Our study showed that there was a significant association between the severity of COPD, as measured by the GOLD grade and COPD group, and cognitive impairment in COPD patients.

Table 2: Association of different variables with cognitive impairment.

Variable	Impairment (n)	%	No Impairment (n)	%	p-value
Gender:					
Male	30	44.78%	25	37.31%	0.03
Female	12	17.91%	0	0.00%	
Age Slabs:					
25 to 34 years	0	0.00%	5	7.46%	0.001
35 to 44 years	6	8.96%	6	8.96%	
45 to 54 years	16	23.88%	4	5.97%	
55 to 64 years	20	29.85%	8	11.94%	
65 years & Over	0	0.00%	2	2.99%	
Addiction:					
Smoking	14	20.90%	21	31.34%	0.122
No Smoking	28	41.79%	4	5.97%	
Exposure:					
Coal/Wood Cooking	21	31.34%	2	2.99%	0.002
Chemical fuel	1	1.49%	2	2.99%	
Aviation fuel	0	0.00%	2	2.99%	
No Exposure	20	29.85%	19	28.36%	
Socioeconomic status:					
Lower	14	20.90%	2	2.99%	0.001
Middle	24	35.82%	12	17.91%	
Upper	4	5.97%	11	16.42%	
Education level:					
Illiterate	22	32.84%	0	0.00%	0.000
Primary	2	2.99%	0	0.00%	
Secondary	6	8.96%	0	0.00%	
Higher Secondary	6	8.96%	6	8.96%	
Higher	6	8.96%	19	28.36%	
Comorbidity:					
Asthma	2	2.99%	0	0.00%	0.046
Diabetes mellitus	6	8.96%	0	0.00%	
Diabetes mellitus, Hypertension	4	5.97%	0	0.00%	
Hypertension	8	11.94%	4	5.97%	
No comorbid	22	32.84%	21	31.34%	
BMI:					
Underweight (< 18.5)	0	0.00%	2	2.99%	0.214
Normal Weight (18.5 to 24.9)	28	41.79%	15	22.39%	
Overweight (25 to 29.9)	10	14.93%	4	5.97%	
Obese (≥ 30)	4	5.97%	4	5.97%	

Patients with more severe COPD are more likely to experience cognitive impairment. The finding is similar to another study.¹⁸ Additionally, specific patterns of cognitive deterioration, such as a decline in verbal memory tasks and compromised executive functions, have been observed in

patients with COPD, which can further impact their ability to perform daily activities.

By addressing cognitive impairment alongside respiratory symptoms, healthcare providers can better manage COPD patients. Additionally, it is important to recognize and address the psychosocial and emotional needs of COPD patients, as cognitive impairment can also affect their mental well-being and quality of life. Older patients with COPD and their families require that clinicians supplement guideline-recommended care with treatment decision making that takes into account. Further research in this area is warranted to fully understand the underlying mechanisms and to develop targeted interventions for this vulnerable population.

CONCLUSION

The study's results underscore the need for a holistic approach to the management and treatment of COPD, considering both pulmonary and extrapulmonary complications such as cognitive impairment.

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Table 3: Gold Grade & COPD Group Vs cognitive impairment.

		Normal	Mild	Moderate	Severe	Total
Gold-Grade	Mild	2 (3.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (3.0%)
	Moderate	15 (22.4%)	16 (23.9%)	2 (3.0%)	4 (6.0%)	37 (55.2%)
	Severe	6 (9.0%)	6 (9.0%)	12 (17.9%)	0 (0.0%)	24 (35.8%)
	V Severe	2 (3.0%)	0 (0.0%)	2 (3.0%)	0 (0.0%)	4 (6.0%)
Total		25 (37.3%)	22 (32.8%)	16 (23.9%)	4 (6.0%)	67 (100%)
COPD-Group	A	13 (19.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	13 (19.4%)
	B	8 (11.9%)	6 (9.0%)	4 (6.0%)	2 (3.0%)	20 (29.9%)
	E	4 (6.0%)	16 (23.9%)	12 (17.9%)	2 (3.0%)	34 (50.7%)
	Total	25 (37.3%)	22 (32.8%)	16 (23.9%)	4 (6.0%)	67 (100%)

- Dobric A, De Luca SN, Spencer SJ, Bozinovski S, Saling MM, McDonald CF, et al. Novel pharmacological strategies to treat cognitive dysfunction in chronic obstructive pulmonary disease. *Pharm Therap* 2022;233:108017.
- Pierobon A, Ranzini L, Torlaschi V, Sini Bottelli E, Giardini A, Bruschi C, et al. Screening for neuropsychological impairment in COPD patients undergoing rehabilitation. *PLoS One* 2018;13:e0199736.
- Yin M, Wang H, Hu X, Li X, Fei G, Yu Y. Patterns of brain structural alteration in COPD with different levels of pulmonary function impairment and its association with cognitive deficits. *BMC Pulm Med* 2019;19:1-0.
- Wang X, Cui L, Ji X. Cognitive impairment caused by hypoxia: from clinical evidence to molecular mechanisms. *Metabol Brain Dis* 2022;37:51-66.
- Adeyemi OJ, Arif AA, Paul R. Assessing the relationship between measures of healthcare access and functional limitations among individuals with Chronic Obstructive Pulmonary Disease (COPD). *MedRxiv* 2022:2021-12.
- France G, Orme MW, Greening NJ, Steiner MC, Chaplin EJ, Clinch L, et al. Cognitive function following pulmonary rehabilitation and post-discharge recovery from exacerbation in people with COPD. *Resp Med* 2021;176:106249.
- Andrianopoulos V, Gloeckl R, Schneeberger T, Jarosch I, Vogiatzis I, Hume E, et al. Benefits of pulmonary rehabilitation in COPD patients with mild cognitive impairment—A pilot study. *Resp Med* 2021;185:106478.
- Venkatesan P. GOLD COPD report: 2024 update. *Lancet Resp Med* 2024;12:15-6.
- Munari AB, Gulart AA, Araújo J, Zanotto J, Sagrillo LM, Karloh M, et al. Modified medical research council and COPD assessment test cutoff points. *Resp Care* 2021;66:1876-84.
- Hobson J. The Montreal cognitive assessment (MoCA). *Occup Med* 2015;65:764-5.
- Cleutjens FA, Janssen DJ, Ponds RW, Dijkstra JB, Wouters EF. Cognitive-pulmonary disease. *BioMed Res Int* 2014;2014:697825.
- Kłoszewska M, Łyszczarz B, Kędziora-Kornatowska K. Sociodemographic and Health-Related Factors Associated with Severity of Cognitive Impairment in Elderly Patients

REFERENCES

- Simargi Y, Mansyur M, Turana Y, Harahap AR, Ramli Y, Siste K, et al. Risk of developing cognitive impairment on patients with chronic obstructive pulmonary disease: A systematic review. *Medicine* 2022;101:e29235.

- Hospitalized in a Geriatric Clinic. *Brain Sci* 2021;11:170-4.
14. Singh B, Mielke MM, Parsaik AK, Cha RH, Roberts RO, Scanlon PD, et al. A prospective study of chronic obstructive pulmonary disease and the risk for mild cognitive impairment. *JAMA Neurol* 2014;71:581-8.
 15. Chen X, Dong X, Liu J, Liu X, Deng M, Yang Y. Rural–Urban Differences in Mild Cognitive Impairment Among Patients with Chronic Obstructive Pulmonary Disease in ChengDu, China. *Int J Chron Obstruct Pulm Dis* 2023;2497-508.
 16. Kakkera K, Padala KP, Kodali M, Padala PR. Association of chronic obstructive pulmonary disease with mild cognitive impairment and dementia. *Curr Opin Pulm Med* 2018;24:173-8.
 17. Baird C, Lovell J, Johnson M, Shiell K, Ibrahim JE. The impact of cognitive impairment on self-management in chronic obstructive pulmonary disease: a systematic review. *Resp Med* 2017;129:130-9.
 18. Cleutjens FA, Spruit MA, Ponds RW, Vanfleteren LE, Franssen FM, Gijzen C, et al. Cognitive impairment and clinical characteristics in patients with chronic obstructive pulmonary disease. *Chron Resp Dis* 2018;15:91-102.

Clinicopathologic spectrum of colorectal polyps highlighting alarming frequency of pre-neoplastic adenomatous polyps with high grade dysplasia

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Objective: To assess the prevalence of colorectal polyps along with clinicopathological characteristics in a tertiary care hospital.

Methodology: This retrospective study was performed at Histopathology department of Dr. Ziauddin Medical University and Hospital. A total of 356 biopsies from January 2018 to December 2022 (5 years periods) were included along with clinical data of patients. Biopsy tissue samples were stained with Hematoxylin and Eosin stain (H&E) and examined under light microscope to characterize the polyps on histomorphology basis.

Results: Amongst 356 biopsy tissue samples of colorectal polyps, 63.2% were males and 36.8% females. Patients more than 60 years old were 40.16%. Most common clinical symptom was rectal bleeding

(46.34%) and most common site was rectum. Adenomatous polyps were 40.44%, hyperplastic 26.12%, juvenile polyps 25.28%, Inflammatory 7.86% and adenocarcinoma 0.28%. Adenomatous polyps with severe dysplasia were 48.6%; 46.52% showed mild dysplasia and 4.86% showed moderate dysplasia.

Conclusion: Our study highlighted the prevalent clinicopathological features of colorectal polyp in our set of population along with alarming frequency of pre-neoplastic adenomatous polyps. Importance of close surveillance and screening for malignant transformation and prompt surgical removal of adenomatous polyps with high malignant potential is conclusively suggested for timely prevention and treatment.

Keywords: Adenomatous polyp, dysplasia, hematoxylin, eosin stain.

INTRODUCTION

Incidence of colorectal polyps has been increasing all over the globe.¹ Colonic polyps have been reported in 15% to 40% of adult American population.² Prevalence of colorectal polyps in Chinese population is 18.1%.¹ Overall prevalence of colorectal polyps in India was reported to be 10.3% and colonic adenomas were found in 5.4% to 6.7% of Indian population.^{3,4} A study from Pakistan reported incidence of colonic polyp to be 12.5%.⁵ Prevalence of adenomatous polyps is reportedly 13.3% in Chinese population.⁶

Polyps are wart like appendages growing on mucosal surfaces.⁷ Colorectal polyps are categorized as non-neoplastic and neoplastic polyps. Non-neoplastic polyps comprise of hyperplastic, inflammatory and juvenile polyps. Neoplastic polyps are adenomatous polyps, which are further classified as tubulo-villous, tubular and villous.⁸ Juvenile polyps are type of hamartomatous polyps, which mostly occur in first 10 years of age and children present with rectal bleeding as the most frequent clinical complaint.

Adenomatous polyps have potential to transform into colorectal carcinoma. Microscopically, there are 3 variants: tubular (TA), tubulo-villous (TVA), and villous adenomas (VA). If villous component makes of 75% of the polyp histologically along with other mentioned

histological features, then it is known as villous adenoma.⁹

The surge in colorectal carcinoma and the prevalence of colorectal polyps is an alarming situation. Categorizing the prevalent clinicopathological characteristics of colorectal polyps in our population is required for the early assessment of potentially malignant tumors. The aim of this study was to assess the prevalence of colorectal polyps along with clinicopathological characteristics in our institution.

METHODOLOGY

This retrospective study was conducted at Histopathology Department of Dr. Ziauddin Hospital-Karachi from January 2018 to December 2022. Biopsy samples of patients labeled as polyps presenting with clinical symptoms related to lower gastrointestinal tract were included in the study, Patients with recurrent polyps and patients with diagnosed intestinal polyposis and inflammatory bowel diseases, those with already diagnosed colorectal carcinoma and with polypoid carcinoids and lymphoid hyperplasia were excluded from the study.

A total of 356 biopsies were included which were reported as colorectal polyps. Clinical data of the patients was retrieved from the reports. Formalin fixed paraffin

embedded sections of all the biopsy tissue samples were reviewed for histology and exact characterization of the dysplastic polyps. All colorectal polyps were examined with H&E stain. Thin layer of Polystyrene mountant was applied followed by a glass coverslip.¹⁰

Statistical Analysis: Data were analyzed by using SPSS version 24.

RESULTS

Amongst 356 biopsy samples, 63.2% were males and 36.8% females. We categorized ages into four groups; 96 patients were 1 to 20 years old (27%); 49 patients were 21 to 40 years old (13.76%); 68 patients were 41 to 60 years old (19.1%) and 143 patients reported were more than 60 years old (40.16%).

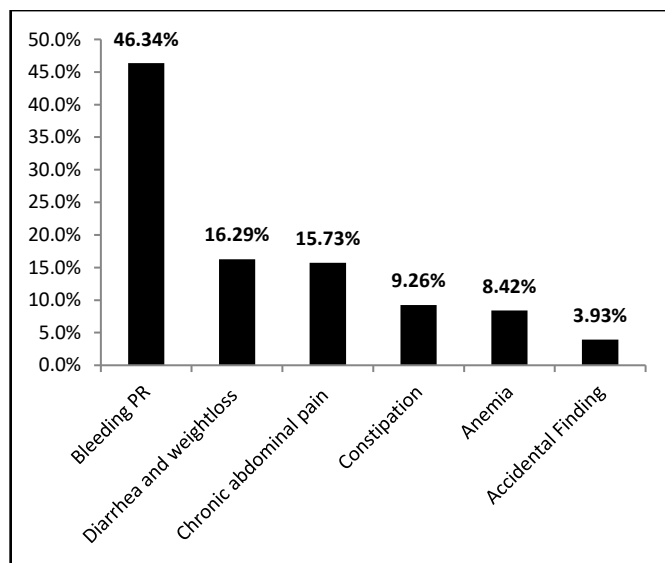


Fig. 1: Discrepancy in most prevalent clinical symptoms among cases.

The majority of cases had complaint of bleeding per rectum while diarrhea and weight loss were second most common clinical symptom (Fig. 1). Most polyps were found in rectum (Fig. 2). Severe dysplasia was evident in most of the adenomatous polyps (Fig. 3). Dysplastic changes observed in reported in over 48% of adenomatous polyps (Fig. 4).

DISCUSSION

We observed that the male gender was more affected, as reported in other studies.¹¹⁻¹³ In contrast to our findings Valarini et al and Nisihara et al, have reported female predominance.^{14,15} In our data, bimodal frequent distribution of age groups was noted as above 60 years and 1 to 20 years were most commonly affected ages, mostly displaying adenomatous polyps in senior age

population as compared to hyperplastic and juvenile polyps in younger ages.

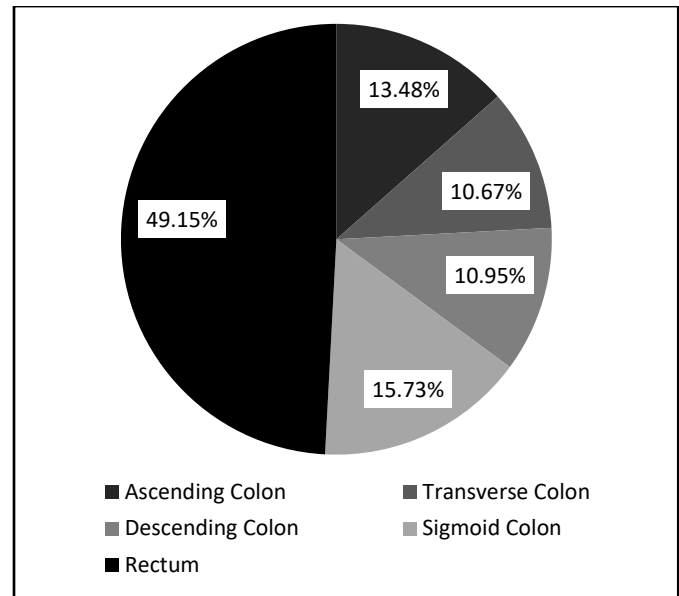


Fig. 2: Sites of colorectal polyps.

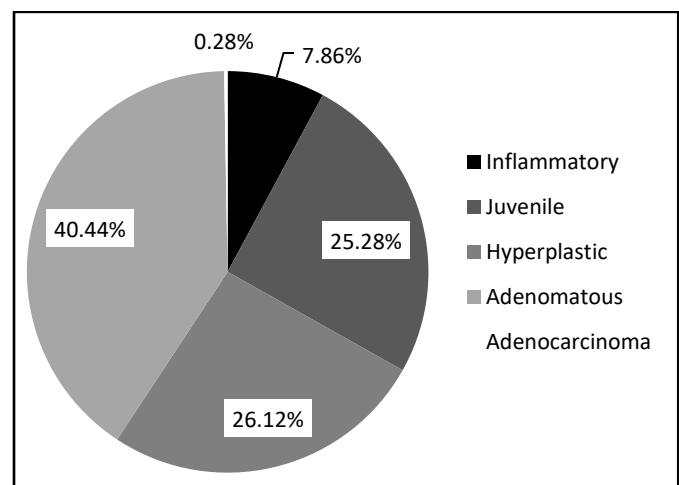


Fig. 3: Different histologically categorized colorectal polyps.

In congruence with our findings, other studies have reported that people above 60 years are most commonly affected.^{7,16} In contradiction to our findings, Goyal reported people younger than 50 years showing higher prevalence of colorectal polyps.¹¹

Clinical features in our series, bleeding per rectum was the most common presentation, which was also observed as most common symptom by Akere et al.¹⁷ Variation in common clinical symptom was noted as chronic abdominal pain as most prevalent symptom by Qari.¹⁸ According to Laird-Fick et al, most common site of colorectal polyps was ascending and transverse colon

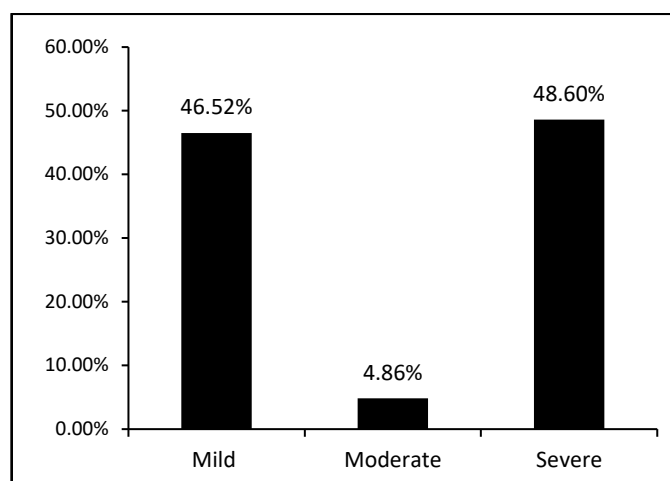


Fig. 4: Grades of dysplastic changes observed in reported Adenomatous polyps.

whereas we found rectum the commonest (49.15%).¹⁹ Similarity in observation was also reported by Wickramasinghe et al.²⁰

In our series, most common histological variant observed was adenomatous polyps (40.44%). Few other studies also found adenomatous polyps as most commonly occurring histological type.^{12,15,17,18} In our series, most of the adenomatous polyps (48.6%) displayed high grade dysplasia, which was very alarming finding.

The presence of dysplastic changes in polyps confers malignant potential and high risk for the patient, which needs meticulous screening for recurrence and primary prevention of colorectal malignancy. Low grade dysplasia was observed in (46.52%). Ahadi et al reported most of the adenomatous polyps displaying low grade dysplasia.¹⁶

There were limitations in histological variants of prevalent Adenomatous polyps, this area shall be considered for further analysis of prevalent histological type of adenomatous polyps.

CONCLUSION

Our study has emphasized the significance of histological examination towards categorization of colorectal polyp and picking up early malignant changes. Most prevalent histological variant in our set of population was pre-neoplastic adenomatous polyps and majority showed high grade dysplasia.

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REFERENCES

- Pan J, Cen L, Xu L, Miao M, Li Y, Yu C, et al. Prevalence and risk factors for colorectal polyps in a Chinese population: a retrospective study. *Sci Rep* 2020;10:6974.
- Bonington SN, Rutter MD. Surveillance of colonic polyps: are we getting it right? *World J Gastroenterol* 2016;22:1925.
- Amarapurkar AD, Nichat P, Narawane N, Amarapurkar D. Frequency of colonic adenomatous polyps in a tertiary hospital in Mumbai. *Ind J Gastroenterol* 2016;35:299-304.
- Jain M, Vij M, Srinivas M, Michael T, Venkataraman J. Spectrum of colonic polyps in a South Indian Urban cohort. *J Digestive Endoscopy* 2017;8:119-22.
- Parkash O, Saeed S, Nadeem M, Hamid S. Not Anymore Uncommon Disease in South Asia: A Spectrum of Colonic Polyps in a Tertiary Care Hospital in Karachi, Pakistan: *Am J Gastroenterol* 2017;112:S67.
- Hong W, Dong L, Stock S, Basharat Z, Zippi M, Zhou M. Prevalence, and characteristics of colonic adenoma in mainland China. *Can Manag Res* 2018;2743-55.
- Soleimaninejad M, Sharifian M. Evaluation of colonoscopy data for colorectal polyps and associated histopathological findings. *Ann Med Surg* 2020;57:7-10.
- Shussman N, Wexner SD. Colorectal polyps and polyposis syndromes. *Gastroenterol Rep* 2014;2:1-5.
- Miller Q, Saeed O, Mesa H. Clinical, pathologic, and molecular-genetic aspects of colorectal polyps. *Gastrointestinal Endoscopy Clinics* 2022;32:313-28.
- Slaoui M, Fiette L. Histopathology procedures: from tissue sampling to histopathological evaluation. *Drug Safety Evaluation: Meth Prot* 2011:69-82.
- Goyal B. Histopathology of Polyps and Cancer of Colorectum: A ten year study from a tertiary care center. *J Gand Med Coll Nep* 2021;14:100-6.
- Abdulhameed TT, Jaff ZO, Maaruf NA. Clinicopathological study and immunohistochemical evaluation of cyclin D1 in adenomatous polyps. *Zan J Med Sci* 2021;25:456-63.
- Basnet D, Makaju R, Gurung RB, Dhakal R. Colorectal polyps: A histopathological study in tertiary care center. *Nepal Med J* 2021;4:414-8.
- Valarini SB, Bortoli VT, Wassano NS, Pukanski MF, Maggi DC, Bertollo LA. Correlation between location, size, and histologic type of colorectal polyps at the

- presence of dysplasia and adenocarcinoma. *J Coloproctol* 2011;31:241-7.
15. Nisihara R, Fudalli F, Turra ML, Malanche RM, Benassi SH, Pimenta AP, et al. Pathological findings of colorectal polyps analyzed in Curitiba-Braz *J Coloproctol* 2017;37:123-7.
 16. Ahadi M, Nejad BK, Farahani ZK, Mollasharifi T, Jamali E, Shalmani HM, et al. Clinicopathologic features of colorectal polyps in Shahid Beheshti University of Medical Sciences (SBMU). *Asian Pacific journal of cancer prevention: APJCP* 2019;20:1773.
 17. Akere A, Ezenkwa US, Oluwasola AO. Clinicopathologic study of colonic polyps in South Western Nigeria. *Niger J Gastroenterol Hepatol* 2019;11:61-6.
 18. Qari YA. Clinicopathological characterization of colonic polyps. *Niger J Clin Pract* 2020;23:1048-53.
 19. Laird-Fick HS, Chahal G, Olomu A, Gardiner J, Richard J, Dimitrov N. Colonic polyp histopathology and location in a community-based sample of older adults. *BMC Gastroenterol* 2016;16:1-7.
 20. Wickramasinghe DP, Samaranayaka SF, Lakmal C, Mathotaarachchi S, Kanishka Lal C, Keppetiyagama C, et al. Types and patterns of colonic polyps encountered at a tertiary care center in a developing country in South Asia. *Anal Cell Pathol* 2014;2014.

Comparison of the psychological distress among medical students of government and private medical universities amid COVID 19 pandemic

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Objective: To evaluate the perceived stress and coping skills of medical students during COVID-19 pandemic.

Methodology: This cross-sectional study included 246 students at RMU and Riphah International University. A finalized questionnaire was disseminated among the students via WhatsApp. Data were analyzed using SPSS 22 and independent t-test and non-parametric test were used for comparison of two groups.

Results: A greater percentage of Riphah students had high stress as compared to RMU. Most of RMU students had moderate stress. Their coping skills varied,

involving both positive and negative, and most of them were satisfied by their institute's response to manage the crisis.

Conclusion: Stress is one of the major factors hindering medical student performance and the coping mechanisms adapted for dealing with it also control the outcome. Developing a resilient attitude towards stress depends upon students' own efforts plus support by their institutes.

Keywords: Covid 19, stress, coping skills.

INTRODUCTION

Stress and its management have always been a great challenge for medical students. The pre-pandemic evidence suggests that medical students' mental health status was poorer than that of general public.¹ In Ethiopia, age, class, year of study, practical attachment, poor social support, financial problems and future career expectations were identified as factors related to perceived stress among medical students.² Coping skills include cognitive and behavioral efforts.³

In December 2019, the first case of a respiratory illness caused by SAR-CoV-2 virus was reported in Wuhan, China.⁴ The virus was confirmed to have reached Pakistan on 26th February, 2020 when two cases were recorded.⁵ It has been shown to have a negative psychological impact on otherwise healthy community causing anxiety, stress and other mental illnesses.⁶ Strict policies such as quarantine and social distancing limit personal freedom, leading to negative effects on mental health and wellbeing.⁷ Being a more vulnerable group and at risk of exposure more than general public, medical students are more prone to mental health issues.^{8,9} For those who had mental health problems during pandemic, coping skills play an important role.¹⁰

This pandemic led to a strong reaction among students who experiences anxiety.¹¹ Health care workers were inefficiently prepared to deal with the stressors.¹² Medical universities have ethical obligations to their students in facilitating adaptive coping.¹³ It is important to study the perspective of medical students to the

COVID-19 pandemic as to perceived stress and coping skills in order to apply required preventions and interventions.¹⁴ The aim of this study was to evaluate the perceived stress and coping skills of medical students during COVID-19 pandemic.

METHODOLOGY

This comparative cross-sectional study included students of two different universities i.e., government and private, studying under different facilities and compared their perceived stress and coping strategies at the same time. The study was approved by IRB (Ref letter no. PSY-32-46-21 dated 15/10/2022). Sample size was calculated using WHO online survey with 95% confidence and 5% and came to be 246. None of these participants were handling the Coronavirus patients.

A finalized questionnaire was disseminated among the students of both universities via WhatsApp. The class representatives from each class of both universities provided student's contact numbers and official email addresses. The respondent students could only proceed to participate in the survey when they had agreed and given their consent by clicking 'yes' option.

The online questionnaire was designed on Google forms after reviewing scientific literature combining dichotomous, Likert response scale and open-ended questions. A pilot study consisting of 10 students was conducted to assess the validity of the questionnaire. According to the feedback received, appropriate changes were made in the questionnaire. The finalized

questionnaire consisted of 48 questions in total divided into 6 sections.

Statistical Analysis: Data were analyzed using SPSS version 22. The independent t-test was used for comparison between two groups and $p < 0.05$ was taken as significant. Non-parametric tests were used to compare different coping mechanisms.

RESULTS

Demographic characteristics of study population are shown in Table 1. The students were asked to define their psychological stress about COVID pandemic. The majority explained their stress as 'episodic stress'. Others had acute or chronic stress. Their stress levels were measured using a perceived stress scale-10.

A total of 22 questions were asked divided broadly into five categories. The factors included transition to online learning and assessment, personal and family's health situation and family's financial situation. The majority was worried about their personal and family's health situation.

Table 1: Demographic details.

Variable		%
Sex	Male	25.3
	Female	74.7
Age	17 to 20	57.3
	21 to 24	41.5
	25 to 29	1.2
Year of study	1 st year	40.8
	2 nd year	15.7
	3 rd year	17.6
	4 th year	21.1
	5 th year	4.8
University	RMU	76.4
	Riphah International University	23.6
Residency	Border	43.4
	Non-border	56.6

The Kruskal Wallis test showed a significant difference between the stress levels of those engaging in negative (denial, negative avoidance and emotional focused), positive (positive avoidance, problem focused, social support and religious coping) and mixed coping mechanisms ($n=124, 9, 113$), $H(2) = 13.155$, ($p=0.001$).

Coping strategies are shown in Table 2. Students from both institutions had moderate stress (Fig. 1).

Table 2: Coping strategies.

Coping Strategies			University	
			Riphah International University	RMU
Appraisal focused	Denial	No	31	105
		Yes	27	83
	Positive Avoidance	No	25	92
		Yes	33	96
	Negative Avoidance	No	28	101
		Yes	30	87
Problem focused		No	14	50
		Yes	44	138
Emotional focused		No	24	106
		Yes	34	82
Social support		No	26	87
		Yes	32	101
Religious coping		No	8	28
		Yes	50	160

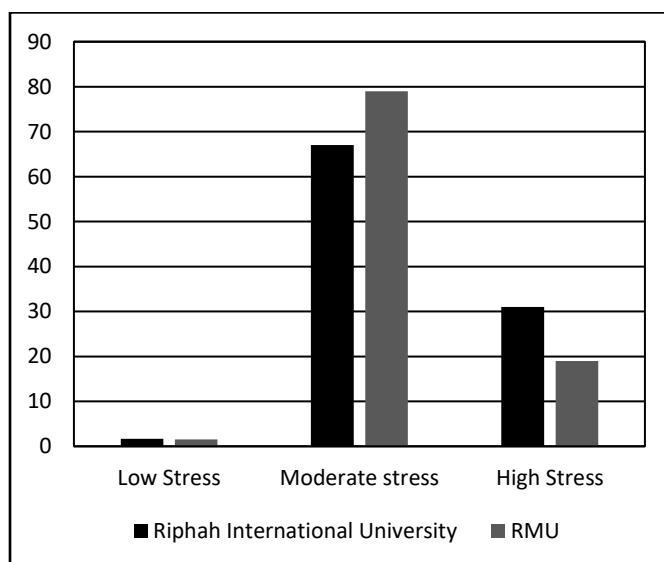


Fig. 1: Representation of PSS.

DISCUSSION

Medical students experience a high level of stress during their undergraduate course,¹⁵ affecting negatively both

their cognitive functioning and learning.¹⁶ A study by Albaha Faculty of Medicine showed that the prevalence of stress among medical students was highest during phase I (85.75%), followed by phase II (85.45%) and phase III (84.1%).¹⁷ The results of this study agree with the Yang et al, who reported an increased stress rate among students due to increased academic workload and fear of contagion during the pandemic.¹⁸ Junior status increases the probability of stress enhancing the need for management programs for students well-being.¹⁹ A systemic study conducted in 2020 regarded them as a 'fragile population' in terms of stress suggesting critical preventive measures.²⁰ Results of this study showed that majority of students had moderate or high stress level not only because of academic burden but also COVID 19, adding a lot to it. The percentage of students having high stress level was greater for private institute whereas greater percentage of government institute student had moderate stress levels.

Several studies have highlighted the need for developing mechanisms to ameliorate the negative effects of stressors, especially by developing resilience. Developing such attitude depends not only on the person's own ability but also on their affiliated institutes.²¹ Findings of this study endorse this concept with student who had greater confidence on their institutes, had less stress levels.

We found that religious coping mechanisms were adapted by most of the students. The second most frequently adapted mechanism was a problem focused in both institutes. One of the concerning factors was the adaptation of negative coping strategies by a significant number of students like denial, blame, substance use, behavioral derangement etc. This concern as well as incidences of rising substance abuse in medical students has been brought out time and again by other studies.²² Personal efforts plus organizational approaches aimed at improving the situation are equally important in dealing with such situations.²³

Although the majority of the students involved in the study had reported having confidence in their respective institutes in handling the situation, some major concerns have also been highlighted. Students have implied their institutes to have a more empathetic attitude towards them and try to understand their circumstances as well. Students had concerns about their attendance issues and not involving them in setting up the schedules of examinations and assessments. The second major problem brought to light was the lack of training of administration and teaching staff about the use of e-platform plus internet connection problems, which created a lot of issues during online learning.

CONCLUSION

We found that medical students were under great stress during COVID 19 pandemic. Dealing with the stressors and developing right coping mechanisms has a lot to do with not only students' behavior and personality but also the role of institute is important.

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REFERENCES

1. Bergmann C, Muth T, Loerbroks A. Medical students' perceptions of stress due to academic studies and its interrelationships with other domains of life: a qualitative study. *Med Educ Online* 2019;24:1. Doi: 10.1080/10872981.2019.1603526
2. Kebede MA, Anbessie B, Ayano G. Prevalence and predictors of depression and anxiety among medical students in Addis Ababa, Ethiopia. *Int J Ment Health Syst* 2019;13:30-6.
3. Devi S. Psychological resilience and coping strategies during Covid-19 pandemic lockdown. *J. Xian Univ. Archit Technol* 2020;12:2925-33.
4. WHO Director-General's opening remarks at the WHO - WHO High Level Dialogue: Expanding COVID-19 Vaccine Manufacture to Promote Equitable Access - World | Relief Web [Internet]. [cited 2021 Sep 28]. Available from: [https://reliefweb.int/report/world/who-director-generals-opening-remarks-wto-who-high-level-dialogue-expanding-covid-](https://reliefweb.int/report/world/who-director-generals-opening-remarks-wto-who-high-level-dialogue-expanding-covid-19)
5. Pakistan confirms first two cases of coronavirus - France 24 [Internet]. [cited 2021 Sep 28]. Available from: <https://www.france24.com/en/20200226-pakistan-confirms-first-two-cases-of-coronavirus>.
6. Asmundson GJG, Taylor S. Corona phobia: Fear and the 2019-nCoV outbreak. *J Anxiety Disord* 2020;70:102196-9.
7. Flesia L, Monaro M, Mazza C, Fietta V, Colicino E, Segatto B, et al. Predicting Perceived Stress Related to the Covid-19 Outbreak through Stable Psychological Traits and Machine Learning Models. *J Clin Med* 2020;9:3350-5.
8. Al-Rabiaah A, Tamsah MH, Al-Eyadhy AA, Hasan GM, Al-Zamil F, Al-Subaie S, et al. Middle East Respiratory Syndrome-Corona Virus (MERS-CoV) associated stress

- among medical students at a university teaching hospital in Saudi Arabia. *J Infect Public Health* 2020;13:687–91.
9. Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. *J Health Soc Behav* 1983;24:385–96.
10. Huang L, Xu F, Liu H. Emotional responses and coping strategies of nurses and nursing college students during COVID-19 outbreak medRxiv 2020. doi.org/10.1101/2020.03.05.20031898
11. Baloran ET. Knowledge, attitudes, anxiety, and coping strategies of students during COVID-19 pandemic. *J Loss Trauma* 2020;25:635–42.
12. Babore A, Lombardi L, Viceconti ML, Pignataro S, Marino V, Crudele M, et al. psychological effects of the COVID-2019 pandemic: Perceived stress and coping strategies among healthcare professionals. *Psychiatry Res* 2020; 293:113366.
13. O’Byrne L, Gavin B, Adamis D, Lim YX, McNicholas F. Levels of stress in medical students due to COVID-19. *J Med Ethics* 2021;47:383–8.
14. Rahman MA, Hoque N, Alif SM, Salehin M, Islam SMS, Banik B, et al. Factors associated with psychological distress, fear and coping strategies during the COVID-19 pandemic in Australia. *Glob Health* 2020;16:1–15.
15. Styles WM. Stress in undergraduate medical education: “the mask of relaxed brilliance.” *Br J Gen Pract* 1993;43:46–7.
16. Dahlin M, Joneborg N, Runeson B. Stress and depression among medical students: a cross-sectional study. *Med Educ* 2005;39:594–604.
17. Atta IS, Almilaibary A. The Prevalence of Stress Among Medical Students Studying an Integrative Curriculum During the COVID-19 Pandemic. *Adv Med Educ Pract* 2022;13:35–8.
18. Yang CI, Chen A, Chen Y. College students’ stress and health in the COVID-19 pandemic: The role of academic workload, separation from school, and fears of contagion. *Plos One* 2021;16:e246694.
19. Byrne D, Buttrey S, Carberry C, Lydon S, O’Connor P. Is there a risk profile for the vulnerable junior doctor? *Ir J Med Sci* 2016;185:603–9.
20. Salazar de Pablo G, Vaquerizo-Serrano J, Catalan A, Arango C, Moreno C, Ferre F, et al. Impact of coronavirus syndromes on physical and mental health of health care workers: Systematic review and meta-analysis. *J Affect Discord* 2020;275:48–57.
21. Maunder RG, Leszcz M, Savage D, Adam MA, Peladeau N, Romano D, et al. Applying the lessons of SARS to pandemic influenza: an evidence-based approach to mitigating the stress experienced by healthcare workers. *Can J Public Health* 2008;99:486–8.
22. Cherkil S, Gardens SJ, Soman DK. Coping styles and its association with sources of stress in undergraduate medical students. *Indian J Psychol Med* 2013;35:389–93.
23. Maunder RG, Lancee WJ, Balderson KE, Bennett JP, Borgundvaag B, Evans S, et al. Long-term psychological and occupational effects of providing hospital healthcare during SARS outbreak. *Emerg Infect Dis* 2006;12:1924–32.

Assessment of parenting psychological stress in raising autistic child

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Objective: To evaluate the effect of the severity of autistic behavior on the psychological well-being and marital relationship of the parents.

Methodology: Our study included 285 parents of 150 children diagnosed with autism. A structured questionnaire with closed-ended questions and a Likert scale was used. Result was analyzed using the Chi-square test to see the association between dependent and independent variables.

Results: We found a significant relationship between the severity of the behavior of autistic children and the anxiety and depression of their parents. Mothers showed higher levels of anxiety and depression

compared to fathers. The study showed a significant relationship between marital satisfaction and the severity of autism.

Conclusion: Mothers displayed significantly higher levels of anxiety and depression compared to fathers, and these heightened emotional states had a more pronounced impact on their marital satisfaction. We recommend the implementation of government-funded programs that offer accessible and specialized mental health support, financial assistance, counseling, and respite care for parents of autistic children.

Keywords: Autism spectrum disorder, depression, anxiety.

INTRODUCTION

Autism spectrum disease (ASD) is a neurodevelopmental defect that is a rapidly growing health problem in children in the first two years of life. It is mainly distinguished by the challenges in social communication and interaction as well as the restricted or stereotyped pattern of behavior.¹ It significantly affects the psychological well-being of parents and causes mental stress, anxiety, and depression in parents of ASD children.²

Current diagnostic criteria DSM V has separated autistic disorder from other disabilities by defining the distinct characteristics of autism such as social and communication skills impairment, and repetitive activities that produce functional disorders in a child's early ages.³ According to the WHO, about one in 100 children is suffering from autism worldwide. The Centers for Disease Control and Prevention (CDC) estimates that autism occurs in 1 in 68 children in the United States.⁴ It is estimated that about 350,000 children in Pakistan have ASD.^{5,6}

It is estimated that 80% of individuals with ASD have been found to have sleeping disorders and there is a high likelihood of developing epilepsy before the age of 5 in children presenting with intellectual disabilities.⁷ It has been found that behavior issues in autism such as self-

harm, hostility, eating non-food items such as paper, chalk, hair, or other inedible items, wandering, restricted and repetitive patterns of behavior negatively impact the psycho-well-being of parents.⁸ The research aimed to assess the psychological issues experienced by parents due to having autistic children.

METHODOLOGY

This cross-sectional study enrolled 285 parents (divorced/married) of 150 children aged between 2-12 years diagnosed with Autism as mild, moderate, and severe and were receiving some form of treatment. Parents who had one autistic child and no child with another type of disability and who had no pre-existing psychological disorders or receiving any therapies such as mindfulness were selected from different public hospitals as well as special schools in twin cities.

We used non-probability purposive and snowball sampling. A structured questionnaire with closed-ended questions and a Likert scale which were based on a literature review. The questionnaires were distributed to parents of 150 diagnosed autistic children aged between 2-12 which included PHQ-9 and GAD-7 to measure anxiety and depression and the Kansas Marital Satisfaction Scale (KMSS) to assess marital satisfaction

in parents. Socio-demographic characteristics such as gender, age and socio-economic status and child characteristics were recorded.

Statistical

Analysis: Chi-square test was used to see the association between dependent and independent variables with SPSS 23. $p < 0.05$ was considered significant.

RESULTS

Of 285 parents, 138 were fathers and 147 were mothers (Table 1). There was a strong correlation between the anxiety and depression levels of parents and the intensity of their child's autism-related behavior.

Compared to fathers, mothers exhibited higher levels of anxiety and sadness because they are typically the ones who care for their special needs child more than the latter. There was a strong correlation between the severity of autism and fathers' marital happiness ($p < 0.05$). Association of severity of autism with parent's anxiety level is shown in Table 2. Association of severity of autism with parent's depression level and association of age with anxiety and depression level are shown in Table 3 and 4, respectively.

Table 1: Demographic data of children, parents, and severity of ASD.

Autistic child characteristics					
Child Age			Gender		
2-7 years	112 (74.7%)		Male	119 (79.3%)	
8-12 years	38 (25.3%)		Female	31 (20.7%)	
Birth order of the child			Severity of ASD		
1st	94 (62.7%)		Mild	84 (56.0%)	
2nd	32 (21.3%)		Moderate	60 (40.0%)	
3rd	24 (16.0%)		Severe	06 (4.0%)	
Parents of autistic children					
Age in years	Father	Mother	Education	Father	Mother
<25	0 (0%)	15 (10.2%)	No schooling	0 (0%)	3 (2.0%)
26-35	55 (36.7)	76 (51.7%)	Matric	3 (2.2%)	15 (10.2%)
36-45	68 (45.3%)	56 (38.1%)	Fsc (FA)	9 (6.5%)	9 (6.1%)
>45	15 (10.0%)	0 (0.0%)	Graduation	33 (23.9%)	64 (43.5%)
Marital status			Masters	90 (65.2%)	Masters
Married	135 (97.8%)	135 (91.8%)	PHD	3 (2.2%)	0 (0.0%)
Divorced	3 (2.2%)	12 (8.2%)	Income		
Job-status			<50000	20 (14.5%)	32 (21.8%)
Employed	138 (100.0%)	46 (31.3%)	50000-100000	41 (29.7%)	40 (27.2%)
Unemployed	0 (0%)	101 (68.7%)			

Table 2: Association of severity of autism with parent's anxiety level.

Parents	GAD 7 Anxiety	Severity of autism			Total	p-value
		Mild	Moderate	Severe		
Fathers	Minimal	18	0	0	18	0.000
	Mild	28	24	0	52	
	Moderate	28	15	3	46	
	Severe	7	12	3	22	
	Total	81	51	6	138	
Mothers	Minimal	9	0	0	9	0.002
	Mild	12	3	0	15	
	Moderate	31	15	0	46	
	Severe	32	42	3	77	
	Total	84	60	3	147	

DISCUSSION

In our study, children age was between 2 and 12 years, which is similar to study by Soltanifar et al, from Iran.⁹ Autism is seen more in boys than in girls,^{11,12} and 62.7% of children with autism were firstborn.¹³ We found that 56% of the children had mild autism, 40% moderate and 4% had severe autism. These results are in contrast to study by Hidalgo et al.¹⁴ Studies have reported that majority of parents fell within the age range of 31-38 years, indicating a slightly older group compared to our

Table 3: Association of severity of autism with parent's depression level.

Parents	PHQ 9 Depression	Severity of autism			Total	p-value
		Mild	Moderate	Severe		
Father	Non-minimal	43	15	3	61	0.000
	Mild	21	21	0	42	
	Moderate	14	6	0	20	
	Moderately Severe	3	9	3	15	
	Total	81	51	6	138	
Mother	Non-minimal	24	6	0	30	0.000
	Mild	24	12	0	36	
	Moderately Severe	30	12	0	42	
	Severe	6	30	3	39	
	Total	84	60	3	147	

Table 4: Association of parental age with anxiety level and depression level.

Parent	Age	GAD 7 Anxiety				Total	p-value		
		Minimal	Mild	Moderate	Severe				
Father	26-35	6	15	21	13	55	0.171		
	36-45	9	31	22	6	68			
	> 45	3	6	3	3	15			
	Total	18	52	46	22	138			
Mother	< 25	3	0	3	9	15	0.008		
	26-35	6	6	30	34	76			
	36-45	0	9	13	34	56			
	Total	9	15	46	77	147			
	Age	PHQ 9 Depression						Total	p-value
		Non-minimal	Mild	Moderate	Moderately Severe	Severe			
Father	26-35	18	18	10	9	0	55	0.058	
	36-45	37	18	10	3	0	68		
	> 45	6	6	0	3	0	15		
	Total	61	42	20	15	0	138		
Mother	< 25	3	0	6	0	6	15	0.028	
	26-35	18	24	22	0	12	76		
	36-45	9	12	14	0	21	56		
	Total	30	36	42	0	39	147		

study.^{15,16} The present study also discovered a significant association between the severity of autism in children and the anxiety and depression levels experienced by both fathers and mothers. Our findings are similar to those of Falk et al.¹⁷

The results of this research do not match with the previous research did not find any significant difference between mothers and fathers in terms of the level of depression.^{18,19} It has been observed that there was a significant association between marital status and parental anxiety, and depression levels. Gau et al, showed that mothers who exhibited higher levels of depression had lower levels of marital satisfaction.²⁰

Our findings contradict those of Langley et al, from the United Kingdom, who did not observe any disparity in the level of marital contentment between fathers and mothers of 89 autistic children.²¹ Millaku and Kraja-Bardhi found no significant association between the age of the parents and the levels of depression and anxiety among them, in contrast to this study.²²

In our study, 65.6% of mothers from families with an income below 50,000 experienced severe anxiety, as reported in prior research conducted by Landon et al.²³ The smaller sample size and lack of control sample for comparison are the limitation.

CONCLUSION

Mothers of children with disabilities often face a higher risk of experiencing physiological distress. Creating a more empathetic and understanding environment can help mothers feel less isolated and better equipped to handle the challenges of caring for a child with a disability, ultimately improving their overall mental and physical health.

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REFERENCES

1. Da Paz NS, Wallander JL. Interventions that target improvements in mental health for parents of children with autism spectrum disorders: A narrative review. *Clin Psychol Rev* 2017;51:1–14.
2. Shtayermman O, Zhang Y. Attachment style and mental health profiles of parents caring for a child with autism: Suicidal ideation, depression and anxiety. *J Autism Dev Disord* 2022;52:4872–82.
3. Okoye C, Obialo-Ibeawuchi CM, Obajeun OA, Sarwar S, Tawfik C, Waleed MS, et al. Early diagnosis of autism spectrum disorder: A review and analysis of the risks and benefits. *Cureus* 2023;Aug;15(8):e43226.
4. Qiu S, Lu Y, Li Y, Shi J, Cui H, Gu Y, et al. Prevalence of autism spectrum disorder in Asia: A systematic review and meta-analysis. *Psychiatry Res* 2020;284:112679.
5. Emad F, Malik AA. Association between Maternal Depression and Autistic Child's Characteristics: A Mediating Role of Treatment. *Acad Edu Soc Sci Rev* 2023;3:453-6.
6. Chiarotti F, Venerosi A. Epidemiology of autism spectrum disorders: A review of worldwide prevalence estimates since 2014. *Brain Sci* 2020;10:274-8.
7. Christensen D, Zubler J. CE: From the CDC: Understanding autism spectrum disorder. *Am J Nurs* 2020;120:30–7.
8. Neuhaus E, Bernier RA, Tham SW, Webb SJ. Gastrointestinal and psychiatric symptoms among children and adolescents with autism spectrum disorder. *Front Psychiatry* 2018;9:515-9.
9. Soltanifar A, Akbarzadeh F, Moharreri F, Soltanifar A, Ebrahimi A, Mokhber N, et al. Comparison of parental stress among mothers and fathers of children with autistic spectrum disorder in Iran. *Iran J Nurs Midwifery Res* 2015;20:93–8.
10. Afrin S, Akter MA, Akter S, Akhter T, Akhter S. Parental Educational Background and Socio-Economic Status of ASD Children in Bangladesh: A Cross Sectional Study. *Med Res* 2021;16:68–75.
11. Zaki RA, Moawad GELNA. Influence of autism awareness on the psychological well-being of mothers caring for their children with autism. *J Nurs Educ Pract* 2016;6.
12. Sedgewick F, Leppanen J, Tchanturia K. Gender differences in mental health prevalence in autism. *Adv Autism* 2021;7:208–24.
13. Galvan JAA, Ramalingam PN, Patil SS, Shobri MAS, Chinna K, Sahrir MS, et al. Mode of delivery, order of birth, parental age gap and autism spectrum disorder among Malaysian children: A case-control study. *Heliyon* 2020;6:e05068.
14. Hidalgo M, Voltas Moreso P, Sans N. Autism spectrum disorder prevalence and associated sociodemographic factors in the school population: EPINED study. *Autism* 2021;25:1999–2011.
15. Chan KKS, Lam CB, Law NCW, Cheung RYM. From child autistic symptoms to parental affective symptoms: A family process model. *Res Dev Disabil*. 2018;75:22–31.
16. Alshahrani MS, Algashmari H. The moderating effect of financial stress and autism severity on development of depression among parents and caregivers of Autistic children in Taif, Saudi Arabia. *J Family Med Prim Care* 2021;10:1227–33.

17. Falk NH, Norris K, Quinn MG. The factors predicting stress, anxiety and depression in the parents of children with autism. *J Autism Dev Disord* 2014;44:3185–203.
18. Benson PR. The impact of child symptom severity on depressed mood among parents of children with ASD: the mediating role of stress proliferation. *J Autism Dev Disord* 2006;36:685–95.
19. Schnabel A, Youssef GJ, Hallford DJ, Hartley EJ, McGillivray JA, Stewart M, et al. Psychopathology in parents of children with autism spectrum disorder: A systematic review and meta-analysis of prevalence. *Autism* 2020;24:26–40.
20. Gau SS-F, Chou M-C, Chiang H-L, Lee J-C, Wong C-C, Chou W-J, et al. Parental adjustment, marital relationship, and family function in families of children with autism. *Res Autism Spectr Disord* 2012;6:263–70.
21. Langley E, Totsika V, Hastings RP. Parental relationship satisfaction in families of children with autism spectrum disorder (ASD): A multilevel analysis: Parental relationship satisfaction. *Autism Res* 2017;10:1259–68.
22. Millaku J, Kraja-Bardhi E. Depression among parents of disabled children. *Int J Innov Res Sci Stud* 2023;6:9–19.
23. Landon J, Shepherd D, Goedeke S. Predictors of satisfaction with life in parents of children with autism spectrum disorder. *J Autism Dev Disord* 2018;48:1640–50.

Assessment of factors affecting nutritional status of adolescent girls studying in Public Schools of Islamabad, Pakistan

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Objective: To assess the prevalence and the factors associated with underweight, overweight and obesity among adolescent girls in public schools of Islamabad using WHO standards.

Methodology: This cross-sectional study included 288 adolescent girls 13–18 years old from classes 7th, 8th, 9th, and 10th of public schools in Islamabad. Anthropometric measurements (height and weight) were carried out to determine the proportion of girls who were underweight (BMI less than 18.5), overweight (BMI 25-30) or obese (BMI >30). Chi-square tests were used to explore the association of categorical outcome variables and associated factors.

Results: Mean age of girls was 14.98±1.41 years. The prevalence of underweight girls was 46%, overweight girls 13.2% and obese girls 7.6%. Maternal education (p=.010) residential status (p=.003), perception of

healthiness (p=.002), perception about figure (p<0.001), buying food from cafeteria (p=0.012), maternal knowledge regarding micro nutrition supplements (p=0.044), age at menarche (p=0.049), respondent education level (p=0.037), occupation of mother (p=0.008), dieting practices (p=0.002), consumption of carbonated drinks (p=0.042) and sedentary life style (p=0.025) were found associated to nutritional status.

Conclusion: The study revealed that all aspects of the girls' environment, including home, schools and community combined to promote unhealthy eating behaviors and lifestyle. This could impact on their diets and long-term health. This study underlines the need for nutrition interventions targeting adolescent girls.

Keywords: Nutritional status, adolescents, underweight, overweight.

INTRODUCTION

Malnutrition refers to insufficiencies, excesses, or imbalances in intake of a person's energy and/or nutrients. Nutritional status is an extremely important indicator for assessing quality of life. Therefore, nutritional status of adolescents should be considered significantly, as it has far-reaching implications for the betterment and development of future generations.¹ WHO defines "adolescence as the segment of life between the ages of 10-19 years.² Almost about half (50%) of the ideal body weight of adult is achieved during adolescent period and failure to gain this can result in growth retardation, malnutrition and even delay the process of sexual maturation in later period of life.³

Poor nutrition usually starts before birth, continues into adolescence, further into adult life. Girls who are chronically malnourished remain malnourished during adolescence, adulthood, and are more likely to have low birthweight (LBW) babies after pregnancy. Conversely, if the mother is obese when she starts her pregnancy she is also at increased risk of complications during pregnancy or delivery, which could result in premature delivery and a LBW baby.⁴ Early intervention plays a very important role in adolescent girls in improving their

nutritional status. This helps in reducing burden of maternal and neonatal mortality and morbidity.⁵

Pakistan has the third highest percentage of stunted children in the world, as 44% of children are stunted and this is mainly due to past malnutrition.⁶ More than 9.6 million children in Pakistan have experienced food deprivation and chronic malnutrition during early childhood.⁸ Beside adolescent pregnancy, adolescence has not been deliberated as of high significance value related to nutrition interventions and needs for lifecycle stage.⁹ The objectives of this study were to evaluate the nutritional status of adolescents girls, to assess the personal and environmental factors affecting their nutritional status and to determine the associations between their socio demographic variables and nutritional status.

METHODOLOGY

This cross-sectional study was conducted in public schools for girls in Islamabad from April 2018 to September 2018 and included 288 adolescent girls ages between 13-18 years. Ethical approval was obtained from the ERC of HAS dated May 24, 2019 and a written consent was obtained from Federal Directorate of

Education Islamabad and school principles. Three girls school F-6 sector were selected. The students were selected using simple random sampling. The total number of selected students in school-1 (S1) was 648, in school-2 (S2) was 320 and in 3rd school was 229 (S3).

The computed sample size was 378 students using WHO sample size calculator with 44% expected prevalence, 95% confidence interval and 5% margin of error. All adolescent girls of grades 7th, 8th 9th and 10th who gave consent were included and who had food allergies or any chronic disease such as insulin dependent diabetes, asthma etc. or physical deformity were excluded from the study.

A questionnaire was self-administered, which was adapted from WHO Global School-Based Student Health Survey 2013 and from a study done in Saudi Arabia.³ It was modified according to local culture and environment after literature review. Questionnaire consisted of three sections i.e. A, B and C. The questions in Section A were related to demographic characteristics, Section B was related to adolescent dietary habits and micronutrients knowledge and intake and Section C had questions related to clinical signs of potential nutrient deficiencies.

Statistical Analysis: The data were analyzed in SPSS version 20. Chi square was used to look for associations of categorical data. $p < 0.05$ was considered significant.

RESULTS

A total of 288 adolescent girls were included in the study with mean age of 14.98 ± 1.41 years and mean age of menarche was 12.69 ± 1.112 years (Table 1). Mean weight of total girls was $43.52 \text{ kg} \pm 10.47$. Mean height of was 146.58 ± 13.82 cm (Table 2).

The age at menarche was associated with weight status and maternal knowledge regarding micronutrients was significantly associated with low BMI (Table 3). However, no significant association was found between vitamin and mineral supplements intake and weight status.

DISCUSSION

The mean age of girls was 14.98 ± 1.41 year and mean height was 146.58 ± 13.82 whereas mean weight of study participants was $43.52 \pm 10.47 \text{ kg}$. The prevalence of underweight was calculated as 45.5%, overweight 13.2% and obese as 7.6%. These findings are similar with a study from India to look for nutritional status of adolescent girls, underweight being the highest in percentage.¹⁵ Respondent education level were ($p = 0.037$) associated with high BMI. However, when means were compared the mean BMI Z score in girls who are studying in 7th & 8th grade was significantly ($p = 0.032$)

Table 1: Socioeconomic and educational status of respondents.

Variables	Number	%
No of Siblings		
0-4	220	76.4
5-10	68	23.6
Residence Status		
Own	171	59.4
Rented	67	23.3
Other	50	17.4
Father's Occupation		
Govt servant	139	48.2
Private job	90	31.2
Own Business	46	15.9
Non- employed	11	3.8
Deceased/Retired	2	0.7
Mother's Occupation		
Govt servant	33	11.45
Private job	13	4.5
Non- employed	240	83.3
Deceased/Retired	2	0.7
Father's Education		
Primary	33	11.5
Secondary	66	22.9
Intermediate	68	23.6
Other	90	31.3
None	31	10.8
Mother's Education		
Primary	35	12.2
Secondary	63	21.9
Intermediate	64	2.2
Other	68	23.6
None	58	20.1

lower as compared to those in 9th & 10th grade. This could be since the girls with increasing age their physical activity reduces due to social and cultural norms. These findings are contradictory to research from rural

Bangladesh that showed no association between education status of girls and stunting.¹⁶ Maternal education level was significantly associated with lower ($p=0.010$) and higher BMI ($p=0.048$). These findings agree with a study from India.¹⁵ Among categories of maternal education, BMI was higher in mothers with no education as compared to mothers who have attained primary or higher education. Higher BMI in girls of uneducated women might be since the research was carried out in urban areas

Table 2: Mean height, weight and BMI according to age.

Age (Years)	Number	Height (cm) (Mean $\pm$ SD)	Weight(kg) (Mean $\pm$ SD)	BMI (Mean $\pm$ SD)
13	58	143.37 $\pm$ 13.03	39.74 $\pm$ 9.90	18.91 $\pm$ 4.24
14	66	148.59 $\pm$ 13.03	42.53 $\pm$ 9.83	19.69 $\pm$ 5.28
15	68	146.76 $\pm$ 14.32	43.36 $\pm$ 7.66	20.51 $\pm$ 4.61
16	53	148.08 $\pm$ 14.75	48.48 $\pm$ 12.98	22.59 $\pm$ 6.68
17	38	145.66 $\pm$ 13.93	44.38 $\pm$ 10.63	22.62 $\pm$ 6.75
18	5	142 $\pm$ 14.94	43.34 $\pm$ 10.80	22.99 $\pm$ 4.73

Table 3: Association between weight categories according to BMI and sociodemographic characteristics.

Variables	Normal	Under	p-	Normal	Over+Obese	p-
	N (%)	N (%)	N (%)	N (%)	N (%)	
Educational level						
Middle	90 (52.3)	82 (47.7)	.364	114 (83.2)	29 (16.8)	.037*
Secondary	67 (57.8)	49 (42.2)		84 (73)	31 (27)	
No. of Children						
0 – 4	114 (51.8)	106 (48.2)	.098	177(80.5)	43 (19.5)	.333
5–10	43 (63.2)	25 (36.8)		51 (75)	17 (25)	
Residence Status						
Owned	93 (54.1)	79 (45.9)	.078	142 (83)	29 (17)	.003*
Rented	31 (46.3)	36 (53.7)		56 (82.4)	12 (17.6)	
Occupation of Father						
Govt servant	72 (51.8)	67 (48.2)	.543	112 (80.6)	27 (19.4)	.874
Private job	52 (57.8)	38 (42.2)		69 (76.7)	21(23.3)	
Owned	27 (58.7)	19 (41.3)		37 (80.4)	9 (19.6)	
Non-employed	6 (54.5)	5 (45.5)		8 (72.7)	3 (27.3)	
Retired	-	2 (100)		2 (100)	-	
Occupation of Mother						
Govt servant	24 (72.7)	9 (27.3)	.100	19 (57.6)	14 (42.4)	.008*
Private job	5 (38.5)	8 (61.59)		12 (92.3)	1 (7.7)	
Non-employed	127 (52.9)	113 (47.1)		195 (81.2)	45 (18.8)	
Deceased	1 (50)	1 (50)		2 (100)		
Father Education						
Primary	16 (48.5)	17 (51.5)	.419	27 (81.8)	6 (18.2)	.407
Secondary	38 (57.6)	28 (42.4)		56 (84.8)	10 (15.2)	

Intermediate	33 (48.5)	35 (51.5)		54 (79.4)	14 (20.6)	
Bachelor/master	49 (54.5)	41 (45.6)		70 (77.8)	20 (22.2)	
None	21 (67.7)	10 (32.3)		21 (67.7)	10 (32.3)	
Mother Education						
Primary	14 (40)	21 (60)		31 (88.6)	4 (11.4)	
Secondary	34 (54)	29 (46)		50 (79.4)	13 (20.6)	
Intermediate	40 (62.5)	24 (37.5)	.010*	54 (84.4)	10 (15.6)	.048*
Bachelor/master	29 (42.6)	39 (57.4)		55 (80.9)	13 (19.1)	
None	40 (69)	18 (31)		38 (65.5)	20 (34.5)	

where processed food is readily available and illiterate mother are not aware of balanced diet and healthy eating. No association was found between both parents working and underweight. Strong association ($p=0.008$) was seen between working mothers with overweight girls. A significantly higher mean Z score of BMI ($p=0.010$) was seen in girls of mother who were government employees when compared to mothers who were working privately and to mothers who are not working at all. This is mainly due to the reason that employed mothers be likely to have different eating and cooking routines which can affect food preferences for family.

Family income and family size was not found associated with either low BMI or high BMI ($p>0.05$). The sequence of girls among siblings showed no association with nutritional status. This finding was contradictory to research where these variables were strongly related to nutritional status of children and adolescents.^{15,17,18} This finding was contradictory to an existing theory that malnutrition is due to poverty. 56% of respondents in this research were not sure about the monthly income of family. A possible source of this contradiction is an inaccurate assessment of the household income. Higher BMI was found associated to residence status ($p=0.005$). Mean BMI z score was significantly lower in girls who were residing in rental houses as compared to girls living in owned. This could reflect the economic condition of family affect nutritional status as finances for food are compromised for finances of living.

A significant association was found between anthropometric indices such as BMI and biological factors such as achievement of menarche and maternal knowledge regarding micronutrient supplements. Average age at menarche among participants was 12.49SD 1.912 years, which is earlier than that reported 15 years.¹⁹ This difference between both populations can be due to environmental dissimilarities and both past and present nutritional status can affect the age at menarche.

CONCLUSION

Malnutrition is widespread not only in young children but in adolescents too and girls are the vulnerable group. Improving nutritional status of adolescent girls can break the vicious cycle of malnutrition. The study shows that unhealthy eating behaviors and lifestyle during adolescence could be due to multiple factors like girls' environment, including home, schools, and community.

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REFERENCES

1. Menon GR, Singh L, Sharma P, Yadav P, Sharma S, Kalaskar S, et al. National Burden Estimates of healthy life lost in India, 2017: an analysis using direct mortality data and indirect disability data. *Lancet Glob Health* 2019;7:e1675-e1684.
2. Akhtar S. Malnutrition in South Asia-A Critical Reappraisal. *Crit Rev Food Sci Nutr* 2016;56:2320-30.
3. Elham AJ. Factors affecting nutritional status and eating behaviours of adolescent girls in Saudi Arabia Elham AL-Jaaly. 2012 [cited 2017 May 1]; Available from: http://discovery.ucl.ac.uk/1370576/2/AL-Jaaly.1370576.Redacted_PhD_thesis.pdf
4. Branca F, Piwoz E, Schultink W, Sullivan L M. Nutrition and health in women, children, and adolescent girls. *BMJ* 2015;351:4173.
5. World Health Organization. (2005). Nutrition in adolescence : issues and challenges for the health sector : issues in adolescent health and development. World

- Health Organization. <https://apps.who.int/iris/handle/10665/43342>
6. Burinato G. Progress report 2013-2015 Results for children in Pakistan STOP STUNTING. [cited 2017 May 1] https://www.unicef.org/pakistan/Stop_Stunting.pdf
7. Gerda verburg forthcoming sun movement coordinator. [cited 2017 Apr 30]; <https://data.unicef.org/wp-content/uploads/2016/06/130565-1.pdf>
8. Mushtaq MU, Gull S, Mushtaq K, Abdullah HM, Khurshid U, Shahid U, et al. Height, weight and BMI percentiles and nutritional status relative to the international growth references among Pakistani school-aged children. *BMC Pediatr* 2012;12:31-7.
9. Melaku YA, Zello GA, Gill TK, Adams RJ, Shi Z. Prevalence, and factors associated with stunting and thinness among adolescent students in Northern Ethiopia: a comparison to World Health Organization standards. *Arch Public Health* 2015;73:1-1.
10. Olney DK, Pedehombga A, Ruel MT, Dillon A. A 2-year integrated agriculture and nutrition and health behavior change communication program targeted to women in Burkina Faso reduces anemia, wasting, and diarrhea in children 3-12.9 months of age at baseline: a cluster-randomized controlled trial. *J Nutr* 2015;145:1317-24.
11. Melese ST, Bedatu G, Kalkidan H. Prevalence of undernutrition and associated factors among preschool children in Jimma town, South West Ethiopia. *Afr J Food Agric Nutr Dev* 2020;20:15954-77.
12. Bhutta ZA, Gupta I, de'Silva H, Manandhar D, Awasthi S, Hossain SM, Salam M. Maternal and child health: is South Asia ready for change? *BMJ* 2004;328:816-9.
13. O'Brien KM, Barnes C, Yoong S, Campbell E, Wyse R, Delaney T, Brown A, et al. School-based nutrition interventions in children aged 6 to 18 Years: An umbrella review of systematic reviews. *Nutrients* 2021;13:4113.
14. Nagar V. Assessment of malnutrition and associated risk factors among 1-5 years children in urban slums of central India. *Group*. 2017;6:24-7.
15. Sharma S, Akhtar F, Singh RK, Mehra S. Relationships between nutrition-related knowledge, attitude, and self-efficacy among adolescents: A community-based survey. *J Fam Med Prim Care* 2019;8:2012-7.
16. Government of Pakistan National Nutrition Survey 2011. [cited 2017 Apr 19]; Available from: <http://pakresponse.info/LinkClick.aspx?fileticket=Ao4s-rwdFVI%3D&tabid=117&mid=752>
17. World Health Organization (WHO). Global school-based student health survey (GSHS); 2019. URL: <https://www.who.int/ncds/surveillance/gshs/en>. 2019 Mar 20.
18. Bhuiyan FR, Barua JL, Kalam KA. Nutritional Status and Nutrition-Related knowledge Among Urban Adolescent Girls in Bangladesh. *Int J Nutr* 2020;6:47-58.
19. Kim H, Choe SA, Lee SJ, Sung J. Causal relationship between the timing of menarche and young adult body mass index with consideration to a trend of consistently decreasing age at menarche. *Plos One* 2021;16:e0247757.

Diagnostic utility of P53 in different grades of glioma

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Objective: To compare the frequency of expression of p53 in different grades of glioma.

Methodology: This descriptive, cross-sectional study was conducted at Pakistan Institute of Medical Sciences from January to December 2019. We included 65 glial neoplasms categorized as astrocytomas, oligodendrogliomas and ependymomas and were graded into low grade and high grade. Brown colored nuclear staining of p53 was interpreted as: - $\leq 10\%$ cells +ve, no staining, 10-25% cells +ve, weak intensity, 26-50% +ve, Moderate intensity and $>51\%$ +ve strong intensity. Data analysis was done using SPSS version 23.

Results: Out of 65 patients, 41 (63.1%) were males and

24 (36.9%) females. Age range was 13-75 years (mean 39.3 ± 14.6). Type of gliomas were as follows: astrocytomas 51 (78.4%), oligodendroglioma and ependymomas 7 each (10.8%). High grade gliomas were 26 (40%) while low grade gliomas were 39 (60%). Frequency of p53 expression in glial neoplasms was 52.3%. Stratification for type and grade of glioma was carried out and no correlation was found.

Conclusion: The frequency of p53 expression in glial neoplasms was 52.3%. The p53 expression was more common among low grade astrocytomas.

Keywords: Astrocytomas, oligodendrogliomas, ependymomas, p53, gliomas.

INTRODUCTION

The worldwide incidence for all primary brain tumors is 4.3 to 18.6 per 100 000 per year.¹ Brain tumors incidence in children ranges from 1.12 to 5.14 cases per 100 000 with the highest incidence in the US.² The most common primary brain tumors in adults are gliomas comprising 81% of all malignant tumors of the brain.³ Incidence of gliomas and glioblastoma in US is 6.61 and 3.19 per 100,000 respectively affecting more males (55%) than females.⁴ In Pakistan, the incidence of intracranial tumors is 12% to 15% with majority as astrocytic tumors.⁵

Glial neoplasms are graded according to WHO, which classify these tumors into four grades namely grade I, II, III, IV. Grades (I and II) are low grade and are well differentiated and grade (III and IV) are high grade and are undifferentiated. This grading system is based on cellularity, atypia, mitotic activity, endothelial proliferation, and necrosis.⁶ Categorization of gliomas into high grade and low grade is important in assessing prognosis and further management. High grade gliomas are resistant to chemotherapy and are therefore difficult to treat.

Multiple immunohistochemical markers are used to aid in the diagnosis of a glial neoplasm particularly p53 gene mutations.⁷ TP53 is a tumor suppressor gene that is critical for regulation of cell cycle, DNA repair and cell death. It is the most mutated gene in human cancers, particularly the gliomas. Mutant p53 has a prolonged

half-life and tends to accumulate intracellularly resulting in its immunohistochemical detection. Jin et al, showed that strong positive expression of p53 was present in 63.8% of high grade and 41.65% of low-grade gliomas.⁸ In this study, the expression p53 was studied in relation to a known prognostic factor of gliomas, that is the grade of tumor.

METHODOLOGY

This descriptive cross-sectional study conducted in the Pathology department of Pakistan Institute of Medical Sciences (PIMS) from January 2019 to December 2019. The sample size is 65 (as calculated by W.H.O sample size calculator), Level of confidence= 95%, anticipated population proportion= 41.65%, absolute precision= 12%. We used nonprobability consecutive sampling. Biopsies and resection specimens of all patients irrespective of age and gender and diagnosed by histopathology as gliomas were included in the study. This included all WHO grades of gliomas (I, II, III, IV). Metastatic tumors to brain and inadequate samples were excluded from the study.

For immunohistochemistry 3–4 μm thick paraffin-embedded tissue section was cut and mounted on slides and dried at 56°C for 30 min. One positive and one negative control were run with each batch of immunostained sections. The tissue samples were thoroughly examined, and total numbers of 500 cells

(150–175 cells per field) were counted and among these, the number of cells which had taken up the stain was counted (Fig. 1).

The p53 positive samples were evaluated semi-quantitatively on a 4-point scale based on the percentage of cells showing p53 staining. The staining criteria for p53 was as follows: when <10% tumor cells showed positive staining, it was interpreted as no staining, for 10–25% it was weak staining only, for 25–50% positive stained cells, the interpretation was positive with moderate intensity, and it was strong intensity when >50% tumor cells showed nuclear staining.⁸

Statistical Analysis: We used SPSS version 23. Chi square test was used to compare the proportion of different p53 expression categories between two Grades of gliomas. Effect modifier such as gender and type were controlled by stratification. Post stratification chi-square test was applied. $p < 0.05$ was considered significant.

RESULTS

A total of 65 patients were included in the study. There were 41 males (63.1%) and 24 females (36.9%). The age range was 13–75 years (mean 39.3 ± 14.6) (Table 1).

Table 1: Distribution of patients by age (n= 65).

Age (Year)	Number	%
13-50	49	75.4
51-75	16	24.6
Total	65	100.0
Mean $\pm$ SD	39.3 $\pm$ 14.6	

Table 3: Stratification for type of glioma with regard to frequency of p53 expression in different types of gliomas (n=65).

Type of glioma	Grade	P53 expression				Total	P value
		$\leq 10\%$	10-25%	10-25%	$\geq 51\%$		
Astrocytoma	High	2	3	4	16	25	0.521
	Low	6	3	3	14	26	
Total		8	6	7	30	51	
Oligodendroglioma	High	1	0	-	0	1	0.459
	Low	2	1	-	3	6	
Total		3	1	-	3	7	
Ependymoma	High	-	-	-	-	-	*
	Low	3	3	-	1	7	
Total		3	3	-	1	7	

The types of gliomas were as follows: Astrocytoma 51 cases (78.4%), Oligodendroglioma and Ependymomas 7 cases each (10.8%). High grade of gliomas was 26 (40%) while low grade gliomas were 39 (60%) (Table 2). Distribution by p53 expression in the glial neoplasms is shown in Table 3.

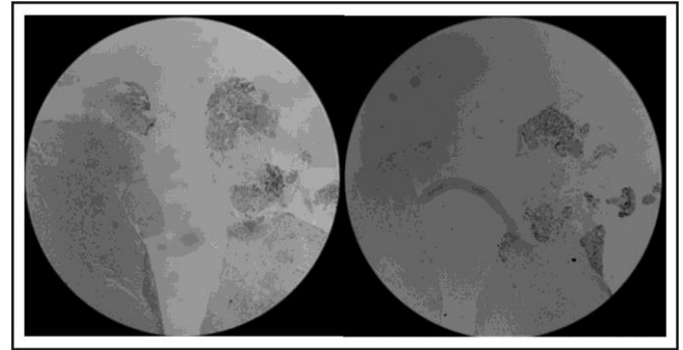


Fig. 1A: (H&E x 100) Pilocytic astrocytoma (low grade), 1B: p53 strong nuclear staining in more than 51% cells.

Table 2: Frequency of p53 expression in different grades of glioma (n=65).

Grade	p53 expression				p value
	$\leq 10\%$	10-25%	25-50%	$\geq 51\%$	
High	3	3	4	16	0.263
Low	11	7	3	18	
Total	14	10	7	34	

DISCUSSION

Gliomas are among the commonest central nervous system tumors all over the world; and each type is derived from a specific glial cell, including astrocytes, oligodendrocytes, and ependymal cells.⁹ The p53 protein is a tumor suppressor that plays key roles in cellular response pathways for cell-cycle control, apoptosis, genomic stability, senescence, differentiation, and angiogenesis.

Inactivation mutations cause alterations of p53 function. The most common p53 mutation is the missense mutation in the DNA-binding domain (DBD). Depending on the p53 status in a tumor, p53 targeted treatments may include preventing the degradation of wild-type p53 (wtp53), suppressing mutant p53 (mutp53), or restoring the wild-type functions of mutp53.¹⁰ p53 over expression is noted in about 50% of gliomas.¹¹ p53 mutation is reported to be associated with a poor prognosis.¹² In our study, 75.5% cases were in the age group of 13-50 years and gliomas were more common in males than females (63.1% vs 36.9%). Wang et al interpreted data of American cancer registry for 16 years and found that 37.8% glioma cases occur up to 50 years of age and they are more common in males.¹³ p53 mutation is reported to be the earliest detectable event in the development of gliomas.¹⁴

In the current study, out of total 65 cases, the frequency of expression of p53 was found to be in 34 (52.3%) gliomas (16 cases of high grade and 18 cases of low grade). Shajani et al, found 28% (46/163) of glioma/glioblastoma cases to have one or more mutations in TP53 and 82% mutations were found in the DNA binding region.¹⁵ Arif et al, from Armed force Institute of Pathology used three immunohistochemical markers including IDH1, ATRX and P53 on low grade glial tumors and found that 37.5% cases of diffuse astrocytomas were positive for p53 mutation, and 62.5% cases were positive for wild type p53 mutation.¹⁶ A study by Chatterjee et al, from Northern India reported 44% cases of gliomas overexpressed p53.¹⁷

In the present study, there was no statistically significant correlation between p53 expression and different grades of glioma ($p=0.263$) as well as between the p53 expression & the types of gliomas ($p=0.521$ and 0.459). Zhang et al found that p53 pathway (including CDKN2A, MDM2 and TP53) was deregulated in almost 80% of high grade gliomas (Glioblastomas) while p53 gene mutation was present in 28% low grade gliomas.¹⁸ Geramizadeh et al, showed that >90% cases of low grade astrocytomas are positive for p53 immunohistochemistry as compared to 4% cases of reactive gliosis.¹⁹

A local study by Ali et al from Aga Khan University Hospital showed immunohistochemically detected overexpression of p53 in 26% of high grade gliomas (Glioblastomas).²⁰ In our study, even though no significant correlation was found between grade and type of glioma with p53 mutation, p53 positivity was observed more in low grade gliomas (18 cases) than in high grade gliomas (16 cases). Bendahou et al, found that p53 mutations are present in both low and high grade astrocytomas and p53 gene mutation along with IDH1

and IDH2 mutations play a key role in the progression of astrocytic neoplasms.²¹

Noor et al, has also documented that there was no significant increase in p53 expression between increasing grades of astrocytoma and they concluded that p53 plays an important role in astrocytoma biology and treatment response, and further p53 mutation types also has effect on gliomagenesis post-treatment.⁷ Guo et al found p53 mutations in 49% glial neoplasms. They used the data in the Genomics of Drug Sensitivity in Cancer (GDSC) database to assess the significance of TP53 mutations in the selection of chemotherapy drugs for glioma and found that glioma cells that harbor a TP53 mutation, were significantly resistance to (5Z)-7-OZ, dabrafenib and nutlin-3a (–) which may not be therapeutically suitable compounds in these cases.²²

CONCLUSION

The frequency of p53 expression in glial neoplasms was 52.3%. The p53 expression is more common among low grade astrocytomas.

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REFERENCES

1. Mesfin FB, Al-Dhahir MA. Gliomas. [Updated 2023 May 20]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK441874/>
2. Subramanian S, Ahmad T. Childhood Brain Tumors. [Updated 2023 Aug 8]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK535415/>
3. Kimberly D, Miller MPH, Quinn T. Brain and other central nervous system tumor statistics. *Can J Clin* 2021;71:381-406.
4. CBTRUS Fact Sheet 2022. CBTRUS Fact Sheet 2022. <https://cbtrus.org/cbtrus-fact-sheet-2022>
5. Enam SA, Shah MM, Bajwa MH. Pakistan Brain Tumour Consortium; Siddiqi S; Pakistan Brain Tumour Consortium Group Names. The Pakistan Brain Tumour Epidemiology Study. *J Pak Med Assoc* 2022;72:S4-S11.
6. Louis DN, Perry A, Reifenberger G. The 2016 World

- Health Organization Classification of Tumors of the Central Nervous System: a summary. *Acta Neuropathol* 2016;13:803–20.
7. Noor H, Briggs NE, McDonald KL. *TP53* Mutation is a Prognostic Factor in Lower Grade Glioma and May Influence Chemotherapy Efficacy. *Cancers* 2021;13:5362.
 8. Jin Y, Xiao W, Song T. Expression, and prognostic significance of p53 in glioma patients: a meta-analysis. *Neurochem Res* 2016;41:1723–31.
 9. Dho YS, Jung KW, Ha J. An Updated Nationwide Epidemiology of Primary Brain Tumors in Republic of Korea, 2013. *Brain Tumor Res Treat* 2017;5:16–23.
 10. Hu J, Cao J, Topatana W. Targeting mutant p53 for cancer therapy: direct and indirect strategies. *J Hematol Oncol* 2021;14:157–9.
 11. Mantovani F, Collavin L, Del Sal G. Mutant p53 as a guardian of the cancer cell. *Cell Death Differ* 2019;26:199–12.
 12. Zhu G, Pan C, Bei JX. Mutant p53 in Cancer Progression and Targeted Therapies. *Front. Oncol* 2020;10: doi.org/10.3389/fonc.2020.595187
 13. Wang GM, Cioffi G, Patil N. Importance of the intersection of age and sex to understand variation in incidence and survival for primary malignant gliomas. *Neuro Oncol* 2022;24:302–10.
 14. Xiong Y, Zhang Y, Xiong S. A Glance of p53 Functions in Brain Development, Neural Stem Cells, and Brain Cancer. *Biology* 2020;9:285–9.
 15. Shajani Z, De Abreu FB, Peterson JD. Frequency of Somatic TP53 Mutations in Combination with Known Pathogenic Mutations in Colon Adenocarcinoma, non–Small Cell Lung Carcinoma, and Gliomas as Identified by Next-Generation Sequencing. *Neoplasia* 2018;20:256–62.
 16. Arif A, Akhtar F, Ahson A. Immunohistochemical Expression of IDH1, ATRX and P53 in Low Grade Diffuse Gliomas at Armed Forces Institute of Pathology, Rawalpindi. *Pak Armed Forces Med J* 2022;72:754–57.
 17. Chatterjee D, Radotra BD. IDH1, ATRX, and BRAFV600E mutation in astrocytic tumors and their significance in patient outcome in north Indian population. *Surg Neurol Int* 2018;9:29–32.
 18. Zhang Y, Dube C, Gibert M Jr. The p53 Pathway in Glioblastoma. *Cancers* 2018;10:297–302.
 19. Geramizadeh B, Kohandel-Shirazi M, Soltani A. A Simple Panel of IDH1 and P53 in Differential Diagnosis Between Low-Grade Astrocytoma and Reactive Gliosis. *Clin Pathol* 2021;14. doi.org/10.1177/2632010x20986168
 20. Ali SMA, Shamim MS, Enam SA. Immunohistochemical Detection and Prognostic Significance of p53, Epidermal Growth Factor Receptor, Murine Double Minute 2, and Isocitrate Dehydrogenase 1 in Glioblastoma Multiforme Patients of Pakistan. *Clin Med Insights Oncol* 2022;16:11795549221119107.
 21. Bendahou MA, Arrouchi H, Lakhlili W, Allam L, Aanniz T, Cherradi N, et al. Computational Analysis of *IDH1*, *IDH2*, and *TP53* Mutations in Low-Grade Gliomas Including Oligodendrogliomas and Astrocytomas. *Cancer Inform* 2020;19:1176935120915839.
 22. Guo CF, Zhuang Y, Chen Y. Significance of tumor protein p53 mutation in cellular process and drug selection in brain lower grade (WHO grades II and III) glioma. *Biom Med* 2020;14. Doi.Org/10.2217/Bmm-2020-0331

Outcomes of cutting Seton in treatment of high peri-anal fistula in Soba University and Ibrahim Malik hospitals, Khartoum, Sudan

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Objective: To evaluate and understand the outcomes and efficacy of cutting Seton technique, widely used for high peri-anal fistulas.

Methodology: This hospital-based cross-sectional study was conducted at Soba University and Ibrahim Malik hospitals, encompassing 60 patients diagnosed with peri-anal fistulas from July to December 2022. Demographics, comorbidities, incontinence, surgical procedures, and diagnostic modalities were documented and analyzed to understand the clinical characteristics and outcomes of the cutting Seton technique.

Results: Out of 60 patients, 83.3% were males and 16.7% females, with an average age of 37.5 years. The majority had discharge history (88.3%), and 40% presented with comorbidities. Park's classification was used to categorize fistula types, revealing predominance

in intersphincteric (36%) and transsphincteric (22%) locations. Cutting Seton success rate of 82%, with discharge duration averaging eight weeks and recurrence at five weeks. No significant differences in postoperative outcomes were found relative to the material used for Seton or the timing of Seton removal.

Conclusion: The study affirms the efficacy of the cutting Seton method in managing high peri-anal fistulas with a high success rate and manageable recurrence. The findings necessitate tailored patient selection and underscore the importance of comorbidities and clinical characteristics in determining treatment outcomes.

Keywords: Peri-anal fistula, cutting Seton, clinical outcomes, comorbidities, surgical treatment, high peri-anal fistula.

INTRODUCTION

Peri-anal fistulas are common colorectal conditions characterized by their complex anatomy and diverse etiology, these fistulas pose a surgical challenge, necessitating a nuanced understanding of anorectal physiology and surgical technique to manage effectively. High peri-anal fistulas, which traverse the upper part of the anal sphincter complex, are especially problematic due to their potential to compromise sphincter integrity and the high risk of postoperative recurrence and incontinence.^{1,2}

The management of high peri-anal fistulas requires a delicate balance between eradicating the fistulous tract and preserving anal sphincter function. Traditional surgical methods, such as fistulotomy, while effective in treating low-type fistulas, are less suitable for high peri-anal fistulas, because of the increased risk of compromising continence. Consequently, sphincter-sparing techniques, including the Seton placement, have gained prominence. The cutting Seton technique offers a gradual method of fistula tract fibrosis and division, aiming to mitigate the risk of immediate sphincter damage and maintain continence.^{3,4}

Despite its widespread use, the literature presents variable outcomes for the cutting Seton technique, with

success rates fluctuating based on fistula complexity, patient demographics, and underlying health conditions.⁵ Furthermore, the recurrence rate and postoperative continence status remain pivotal concerns, with studies showing a broad range of results.⁶ This variability underscores the need for more comprehensive research to delineate the factors influencing the success and failure of the cutting Seton technique, especially in diverse patient populations.⁶

In the Sudanese context, where healthcare resources and access to specialized colorectal services might be limited, understanding the local patient outcomes and procedural efficacy is critical. Considering the potential variations in patient demographics, lifestyle, and healthcare infrastructure between regions, studies conducted in settings like Sudan are essential to provide insights into the effectiveness and adaptability of the cutting Seton technique in different global contexts.⁷

Therefore, this study aimed to investigate the outcomes of the cutting Seton technique in the treatment of high peri-anal fistulas within the patient population of Soba University and Ibrahim Malik hospitals. It seeks to assess the procedure's efficacy, recurrence rate, and impact on continence, providing valuable data to inform both local and international surgical practices.

METHODOLOGY

Study design and setting: This study was a hospital-based retrospective study conducted at Soba University and Ibrahim Malik hospitals in Sudan. The study was approved by IRB of Soba University and Ibrahim Malik hospitals. These institutions are recognized for their specialized colorectal services, making them appropriate sites for investigating high peri-anal fistula treatments. The study period spanned from July to December 2022, allowing for the comprehensive collection and analysis of data regarding the outcomes of cutting Seton in the treatment of high peri-anal fistulas.

Participants: Inclusion criteria were adults aged 18 years and above, diagnosed with high peri-anal fistulas, and treated with the cutting Seton technique. Exclusion criteria included patients with low peri-anal fistulas, those with fistulas secondary to inflammatory bowel diseases, and patients who underwent other forms of surgical management for their fistulas.

Intervention: The cutting Seton technique was performed as per the standardized protocol adopted by the surgical departments at the hospitals. The procedure involved the placement of a Seton (silk, rubber band, or other biocompatible materials) through the fistula tract, which was gradually tightened over time to facilitate fistula tract fibrosis and eventual cutting.

Outcome measures: The primary outcome was the success rate of the cutting Seton technique, defined as complete fistula closure without recurrence at six months post-procedure. Secondary outcomes included the incidence of postoperative complications, such as infection, anal incontinence, and pain, as well as the time to Seton removal and the rate of fistula recurrence.

Data collection: Demographic and clinical data were retrospectively extracted from the patients' medical records. This included age, gender, fistula characteristics (location, type, and classification based on Park's classification), history of prior anal surgeries, and comorbid conditions. Detailed records of the surgical procedure, post-operative outcomes, and any complications or recurrences were also collected.

Statistical Analysis: Data were analyzed using SPSS version 26. Descriptive statistics were used to summarize the demographic and clinical characteristics of the study population. The success rates and complications were calculated as proportions. Chi-square and Fisher's exact tests were utilized for categorical data to explore the associations between patient characteristics, the type of Seton used, and the treatment outcomes. $p < 0.05$ was considered statistically significant.

RESULTS

Sociodemographic characteristics: The study included 60 patients who underwent cutting Seton treatment for high peri-anal fistulas, predominantly male (83.3%). The age distribution highlighted a median group of 30-39 years (33.3%). Detailed demographic and clinical characteristics are presented in Table 1.

Medical history and preoperative assessment: Most patients had a history of peri-anal discharge (88.3%), and a significant portion had undergone previous peri-anal surgeries (28.3%). Comorbidity prevalence was 40%, with diabetes mellitus being the most common (24%) (Table 2).

Table 1: Demographic and clinical characteristics of patients.

Variable	Number	%
Total Patients	60	100
Gender: Male	50	83.3
Age Range (30-39 years)	20	33.3

Table 2: Medical history and preoperative assessment of patients.

Variable	Number	%
History of Discharge	53	88.3
Prior Peri-anal Surgeries	17	28.3
Comorbidities:	24	40
- Diabetes Mellitus	14	23.3
- Hypertension	2	3.3

Table 3: Diagnostic findings and fistula classification.

Diagnostic/Classification	Number	%
Sigmoidoscopy	58	96.7
Fistulogram	52	86.7
MRI Fistulogram	42	70
Type of Fistula:		
- Intersphincteric	22	36.7
- Transsphincteric	13	21.6
- Extrasphincteric	13	21.6
- Suprasphincteric	12	20.1

Diagnostic findings and fistula classification: Diagnostic procedures primarily included sigmoidoscopy

(96.7%), fistulogram (86.7%), and MRI fistulogram (70%). The fistula types, classified according to Park's system, showed a higher incidence of intersphincteric fistulas (36.7%) (Table 3).

Table 4: Surgical outcomes and postoperative assessment.

Outcome	Number	%
Postoperative Pain	59	98.3
Postoperative Irritation	59	98.3
Postoperative Discharge	57	95.0
Cutting Seton Success Rate	49	82.0

Surgical outcomes: Rubber bands were the most commonly used material for Setons (70%). The postoperative period was marked by significant pain and irritation in 98.3% of patients, with an 82% success rate for the cutting Seton procedure. Postoperative outcomes are detailed in Table 4.

DISCUSSION

This study's exploration of the cutting Seton technique for high peri-anal fistulas presents a significant success rate of 82%, a figure that aligns with the upper range of outcomes reported in the literature, suggesting that with optimal patient selection and meticulous technique, high efficacy can be achieved.^{8,9} The predominance of male patients and the median age group in our study mirror global epidemiological trends, indicating a demographic susceptibility that warrants further investigation.¹⁰

The success rate observed in our cohort is consistent with prior studies, where rates vary between 70% and 95%.¹¹ Notably, our study's low recurrence rate (3.3%) emphasizes the cutting Seton's effectiveness in durable fistula resolution. However, this contrasts with some reporting higher recurrence rates, hinting at the possibility of methodological or demographic influences affecting outcomes.¹² The demographic skew towards males and the specific age group underscores a possible pattern in fistula prevalence, potentially influenced by lifestyle, occupational hazards, or genetic predispositions, meriting deeper epidemiological scrutiny.¹³ The study's findings reinforce the cutting Seton's role in managing high peri-anal fistulas, emphasizing its balance between efficacy and sphincter preservation. This balance is imperative in maintaining postoperative continence and quality of life, a primary concern in fistula management.^{14,15} The association of comorbidities, particularly diabetes mellitus, with fistula patients in our study raises the need for comprehensive preoperative

evaluations to tailor surgical interventions and improve outcomes.¹⁶

Our research, while vigorous in its clinical focus, encounters limitations typical of retrospective analyses, including potential selection biases and the constraints of available medical records. The single-center design may limit the generalizability of our findings, necessitating multicentric studies to validate and expand upon our results. Furthermore, the relatively small sample size underscores the need for larger-scale studies to refine the understanding of cutting Seton's efficacy and optimize procedural protocols.

Future investigations should aim to establish multicenter trials with larger and more diverse patient populations to explore the nuances of demographic influences on treatment outcomes. Prospective designs could provide more controlled environments to assess the cutting Seton technique's efficacy, comparing it with emerging surgical innovations. Additionally, exploring the interplay between patient comorbidities and surgical success could yield insights into preoperative care strategies that enhance postoperative results.

CONCLUSION

In conclusion, the cutting Seton technique stands as a valuable method in the surgical arsenal against high peri-anal fistulas, with our study's findings bolstering its reputation for efficacy and safety. However, the journey towards optimal management of peri-anal fistulas is ongoing, with future research set to refine surgical techniques, enhance patient selection criteria, and improve overall patient care and outcomes in this complex clinical field.

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REFERENCES

- Varsamis N, Kosmidis C, Chatzimavroudis G, Sapalidis K, Efthymiadis C, Kiouti FA, et al. Perianal fistulas: a review with emphasis on preoperative imaging. *Adv Med Sci* 2022;67:114-22.
- Cheung XC, Fahey T, Rogers AC, Pemberton JH, Kavanagh DO. Surgical management of idiopathic perianal fistulas: a systematic review and meta-analysis. *Digestive Surg* 2021;38:104-19.
- Kraima AC, West NP, Roberts N, Magee DR, Smit NN, Van de Velde CJ, et al. The role of the longitudinal muscle in the anal sphincter complex: implications for the intersphincteric plane in low rectal cancer surgery? *Clinical Anatomy* 2020;33:567-77.
- Muro S, Kagawa R, Habu M, Ka H, Harada M, Akita K. Coexistence of dense and sparse areas in the longitudinal smooth muscle of the anal canal: Anatomical and histological analyses inspired by magnetic resonance images. *Clinical Anatomy* 2020;33:619-26.
- Ratto C, Marra AA, Parelo A, De Simone V, Campenni P, Litta F. Would Surgeons Like to Be Submitted to Anal Fistulotomy? An International Web-Based Survey. *J Clin Med* 2023;12:825-9.
- Melo IM, Vargas ED, Briceño JdC, Chiantera D, Pérez MC, Bonilla EC, et al. Multiple Scale of Complexity for Anorectal Fistulas. *World J Colorectal Surg* 2022;11:101-7. Al Sebai OI, Ammar MS, Mohamed SH, El Balshe MA. Comparative study between intersphincteric ligation of perianal fistula versus conventional fistulotomy with or without seton in the treatment of perianal fistula: a prospective randomized controlled trial. *Ann Med Surg* 2021;61:180-4.
- Putranto AS, Layardi WJ. Management of Complex Anal Fistula. *N Ropanasuri J Surg* 2022;7:11-6.
- Force PbTSPT, Whiteford MH, Kilkenny J, Hyman N, Buie WD, Cohen J, et al. Practice parameters for the treatment of perianal abscess and fistula-in-ano (revised). *Dis Colon Rectum* 2005;48:1337-42.
- Sainio P, editor *Fistula-in-ano in a defined population. Incidence and epidemiological aspects. Annales chirurgiae et gynaecologiae*; 1984.
- Garcia-Aguilar J, Belmonte C, Wong W, Goldberg D, Madoff RD. Cutting seton versus two-stage seton fistulotomy in the surgical management of high anal fistula. *J Brit Surg* 1998;85:243-5.
- Van Onkelen R, Gosselink MP, Schouten W. Is it possible to improve the outcome of transanal advancement flap repair for high transsphincteric fistulas by additional ligation of the intersphincteric fistula tract? *Dis Colon Rectum* 2012;55:163-6.
- Lunniss P, Phillips R. Anatomy and function of the anal longitudinal muscle. *Brit J Surg* 1992;79:882-4.
- Sarveazad A, Bahardoust M, Shamseddin J, Yousefifard M. Prevalence of anal fistulas: a systematic review and meta-analysis. *Gastroenterol Hepatol From Bed to Bench* 2022;15:1-7.
- Nelson R, Manuel D, Gumienny C, Spencer B, Patel K, Schmitt K, et al. A systematic review and meta-analysis of the treatment of anal fissure. *Techniques Coloproctol* 2017;21:605-25.
- Zanotti C, Martinez-Puente C, Pascual I, Pascual M, Herreros D, García-Olmo D. An assessment of the incidence of fistula-in-ano in four countries of the European Union. *Int J Colorectal Dis* 2007;22:1459-62.

Comparison of perineal tears among patients delivered vaginally in their first ongoing term pregnancies with and without episiotomy

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Objective: To evaluate the frequency of perineal tears among patients delivered vaginally in their first ongoing term pregnancies with and without episiotomy.

Methodology: This Randomized Controlled Trial was carried out at Department of Obstetrics & Gynecology, Imran Idrees Teaching Hospital, Sialkot from 1st January 2023 to 30th June 2023. WE included 120 females from labor room. They were randomly divided in two groups. In group 1, patients underwent vaginal delivery with episiotomy. In group 2, they underwent vaginal delivery without episiotomy. During delivery, vaginal examination was done to assess the presence of

all degrees of perineal tears.

Results: Mean age of females in Groups 1 was 27.55±3.37 years and in Group 2 it was 27.58±3.29 years. We found that 43.33% in Group 1 and 23.33% in Group 2 had perineal tears whereas 56.67% in Group 1 and 76.67% in Group 2 had no perineal tears (p=0.02).

Conclusion: Women in their first pregnancies, during term vaginal birth, the rate of perineal tears was considerably greater in those undergoing episiotomy than no such incision.

Keywords: Vaginal delivery, episiotomy, perineal tears.

INTRODUCTION

The genitourinary system often suffers major and minor injuries during vaginal births. Several strategies for preventing perineal damage have been tested and analyzed.¹ The cervix, vagina, vulva, perineum, labial, peri clitoral and periurethral areas are all vulnerable to trauma. Less common is the increased risk of pelvic floor injury, fecal and urinary incontinence, pain, and sexual dysfunction.²

It is anticipated that between 53 and 79% women may bleed during vaginal birth, most often in the perineal region.³ The trend does not show benefit from the practice of doing an episiotomy to avoid brachial plexus damage in cases of shoulder dystocia, despite prior recommendations for this procedure.⁴ One study showed that among females who underwent vaginal delivery, frequency of perineal tears was more common in females with episiotomy as compared to females without episiotomy (78.1% vs. 47.6%, p<0.001).⁵

Another trial showed that among females who underwent vaginal delivery, frequency of perineal tears was less in females with episiotomy as compared to females without episiotomy (26% vs. 52%, p<0.001).⁶ Another study showed that among females who underwent vaginal delivery, there was no difference in occurrence of perineal tears with or without episiotomy (2.0% vs. 1.3%, p>0.05).⁷ Aim of this study was to compare the frequency

of first-, second-, third- and fourth-degree perineal tears with and without episiotomy in primigravida females undergoing vaginal delivery at term.

METHODOLOGY

This Randomized Controlled Trial was done at Department of Obstetrics & Gynecology, Imran Idrees Teaching Hospital, Sialkot from 1st January 2023 to 30th June 2023. The study was approved by IRB of Sialkot Medical College (Ref: SMC/IIIRS/IRB-07). An informed consent was given by all patients.

Sample size of 120 cases; 60 cases in each group is calculated with 90% power of test, 5% level of significance and taking expected percentage of perineal tears i.e. 52% without episiotomy and 26%⁶ with episiotomy in primigravida females undergoing delivery at term. We included 120 females of age 18-35 years presenting at term (gestational age >37 weeks on LMP) in active labor (>3 contractions within 10 minutes, cervical dilatation >4cm). Females with gestational or chronic hypertension, diabetes, liver disease, renal insufficiency, cardiac disease, anemia, asthma were excluded from this study.

Name, age, gestational age, and BMI information were recorded. Using a lottery system, the women were divided into two groups. Group 1 received episiotomy and group 2 underwent vaginal delivery without

episiotomy. Vaginal examination was done to assess the presence of perineal tears. It was classified if the woman in second stage labor had a spontaneous rupture of the skin and other soft tissue structures separating the vagina from the anus.

Statistical Analysis: The data were analyzed through SPSS version 21. All perineal tears were compared between the two groups using the chi-square test, with a significance level set at $p\text{-value} \leq 0.05$.

RESULTS

Mean age was 27.55 ± 3.37 years. Gestational age and BMI are shown in Table 1. We found that 26 (43.33%) in Group-1 and 14 (23.33%) in Group-2 had perineal tears whereas 34 (56.67%) in Group-1 and 46 (76.67%) in Group-2 had no findings of perineal tears, p value was 0.02 (Table 2).

Table 1: Baseline characteristics of participants (n=120).

Variable	Group-1 (n = 60)		Group-2 (n = 60)	
	F	%	F	%
Number	60	100	60	100
Age (in years)	27.55 ± 3.37		27.58 ± 3.29	
18-30	47	80	48	78.33
31-35	13	20	12	21.67
Gestational age (weeks)	39.35 ± 1.02		39.55 ± 1.12	
>37-40	51	85	49	81.67
>40	9	15	11	18.33
BMI (kg/m^2)	29.8 ± 2.72		29.6 ± 2.68	

Table 2: Frequency of perineal tears with and without episiotomy (n=120).

Perineal tears	Group-1 (n = 60)		Group-2 (n = 60)		P-value
	F	%	F	%	
Yes	26	43.33	14	23.33	0.02
No	34	56.67	46	76.67	

DISCUSSION

There is conflicting evidence supporting the use of episiotomy with operative vaginal deliveries.⁸ The role of episiotomy about prevention of anal sphincter injuries is

under discussion. The recently published guideline of WHO states that role of episiotomy during operative vaginal deliveries remains to be established.

Recent large observational studies have pointed out that adequately performed mediolateral episiotomies may play an important role in the prevention of anal sphincter injuries during operative vaginal deliveries.⁹ The rate of births that occur in hospitals is 50% in the United States, 30% in Sweden, and 53% in England.^{10,11} Episiotomies are thought to lessen the likelihood of perineal tears of third and fourth degrees.^{12,13} Episiotomies have been linked to greater rates of blood loss, infection, and third- and fourth-degree perineal injury, although there is insufficient evidence to recommend its regular usage.^{14,15} This study may help to improve our practice and in future we may recommend taking steps to prevent perineal tears in primigravida.

Our study showed that frequency of perineal tears was 43.33% in Group-1 and 23.33% in Group-2 whereas 56.67% in Group-1 and 76.67% in Group-2 ($p=0.02$). One study showed that among females who underwent vaginal delivery, frequency of perineal tears was more common in females with episiotomy as compared to females without episiotomy (78.1% vs. 47.6%, $p<0.001$).⁵ The frequency of perineal tears was lower in our study.

Another trial showed that among females who underwent vaginal delivery, frequency of perineal tears was less in females with episiotomy as compared to females without episiotomy (52% vs. 26%, $p<0.001$).⁶ Our results are similar. But one study showed that among females who underwent vaginal delivery, there is no difference in occurrence of perineal tears in females with or without episiotomy (2.009% vs. 1.339%, $p>0.05$).⁷ These findings do not correspond to our findings.

Manzanares et al found that women in the perineal trauma group were significantly older and mainly attended by a midwife.¹⁶ Fetal birth weight, gestational age, and the use of epidural anesthesia all resulted in the same distribution. The risk of a perineal tear during the next delivery was five times higher for the perineal trauma group (adjusted OR 5.15, 95% CI 3.11-8.54), and the risk of undergoing an episiotomy in the second delivery was three times higher (adjusted OR 3.20, 95% CI 2.19-4.69). They concluded that having an episiotomy in first delivery increases the likelihood of perineal tear or needing an episiotomy in the second delivery, which restricts the regular use of episiotomy. However, the hypothesis of our study that "there is a difference in the frequency of perineal tears with and without episiotomy in primigravida females undergoing vaginal delivery at term" is justified.

CONCLUSION

In primigravida women enduring a term vaginal birth, the rate of perineal tears is considerably greater with episiotomy than no such incision.

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REFERENCES

1. Aasheim V, Nilsen A, Lukasse M, Reinar LM. Perineal techniques during the second stage of labour for reducing perineal trauma. *Cochrane Database Syst Rev* 2011;12(CD006672).
2. Practice Bulletin No. 165. Prevention and Management of Obstetric Lacerations at Vaginal Delivery. *Obstet Gynecol* 2016;128:e1-e15.
3. Haelle T. ACOG: New Recommendations on Obstetric Lacerations 2016 [cited 2016]. Available from: <http://www.medscape.com/viewarticle/865296>.
4. Paris AE, Greenberg JA, Ecker JL, McElrath TF. Is an episiotomy necessary with a shoulder dystocia? *Am J Obstet Gynecol* 2011;205:217.
5. Brohi ZP, Sadaf A, Zohra N, Perveen U. Frequency, and severity of perineal tears in Countess Lady Duffrin Fund Hospital, Hyderabad. *J Pak Med Assoc* 2012;62:803.
6. Farooq S, Farook SM, Abbassi RM. Pattern of perineal tears during vaginal delivery at a public sector University Hospital of Sindh. *Pak J Med Sci* 2010;26:856-9.
7. Sohail N, Badar N, Saleem F, Sehgal S, Iqbal N, Huma N, et al. Episiotomy and Perineal Tears in Primigravidae. *Pak J Med Health Sci* 2010;4:464-7.
8. Okeahialam NA, Wong KW, Jha S, Sultan AH, Thakar R. Mediolateral/lateral episiotomy with operative vaginal delivery and the risk reduction of obstetric anal sphincter injury (OASI): A systematic review and meta-analysis. *Int Urogynecol J* 2022;33:1393-405.
9. Sultan AH, Thakar R, Ismail KM, Kalis V, Laine K, Räisänen SH, et al. The role of mediolateral episiotomy during operative vaginal delivery. *Eur J Obstet Gynecol Reprod Biol* 2019;240:192-6.
10. Sultan AH, Kamm MA, Hudson CN, Bartram CI. Third degree obstetric anal sphincter tears: risk factors and outcome of primary repair. *BMJ* 1994;308:887-91.
11. Fynes M, Donnelly V, Behan M, O'Connell PR, O'Herlihy C. Effect of second vaginal delivery on anorectal physiology and faecal continence: a prospective study. *Lancet* 1999;354:983-6.
12. Moore JE, Witt WP, Elixhauser A. Complicating Conditions Associated with Childbirth, by Delivery Method and Payer, 2011. Healthcare Cost and Utilization Project (HCUP) Statistical Briefs. Rockville (MD): Agency for Healthcare Research and Quality (US); 2006.
13. Henke RM, Wier LM, Marder WD, Friedman BS, Wong HS. Geographic variation in cesarean delivery in the United States by payer. *BMC Pregnancy Childbirth* 2014;14:387.
14. Harkin R, Fitzpatrick M, O'Connell PR, O'Herlihy C. Anal sphincter disruption at vaginal delivery: is recurrence predictable? *Eur J Obstet Gynecol Reprod Biol* 2003;109:149-52.
15. Pavličev M, Romero R, Mitteroecker P. Evolution of the human pelvis and obstructed labor: new explanations of an old obstetrical dilemma. *Am J Obstet Gynecol* 2020;222:3-16.
16. Manzanares S, Cobo D, Moreno-Martínez MD, Sánchez-Gila M, Pineda A. Risk of episiotomy and perineal lacerations recurring after first delivery. *Birth* 2013;40:307-11.

Effect of husband's support on anxiety level of mothers giving birth

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Objective: To analyze correlation of husband's support with the level of anxiety and length of labor in women giving birth.

Methodology: This cross-sectional study included a sample of 60 maternity mothers. Sampling technique used was purposive sampling method. Inclusion criteria were gestational age 37 to <42 weeks and the mother is in a normal delivery process. Data were analyzed by using chi-square.

Results: We found that 100% or 37 respondents with good husband support had a mild level of anxiety compared to husbands who lacked support in the delivery process. There was a correlation between husband's support and the level of anxiety ($p=0.00$).

Conclusion: There was a correlation between husband's support and the level of anxiety.

Keywords: Husband's support, anxiety, normal delivery.

INTRODUCTION

Every woman wants a pregnancy and most will welcome their pregnancy happily. But for some mothers, the first pregnancy will make them confused and even stressful and the process of becoming a mother is very challenging. Childbirth is a physiological process which involves psychosocial and emotional aspects and sometimes causes trauma.

Anxiety and fear will arise when entering labor. The presence of the husband in the delivery process can reduce anxiety and provide peace for the mother in labor.¹ The smooth delivery process can be influenced by physical and psychological conditions in pregnant. A husband can provide attention and be a place to share. Many things affect partners in giving attention, including social status or gender, some women can be strong and able to go through the birth process with the support of their partners.² In Indonesia, there are 373,000 pregnant women, who experience anxiety during childbirth.³ Judging from psychological factors, one of the causes of prolonged labor is the psychological state of the mother. A woman who is very scared, anxious, or even very excited can become tense and have difficulty coping with her contractions. Thus, it is likely that mothers with these conditions will experience a longer and uncomfortable labor process.⁴ One of the human body's responses to stress compensation is to secrete catecholamine hormones, which will directly result in uterine dysfunction.⁵ The anxiety level of pregnant women becomes more acute and intense as the baby's birth approaches.

To overcome the excessive level of anxiety, it is necessary to have family support, including husband's support in dealing with the delivery process. The fact is

that a husband is not always allowed to accompany his wife at the time of birth on the grounds of avoiding infection in the delivery room, as he is considered one of the causes of contamination. However, in the current conditions, this prohibition is increasingly rare, in fact it is more recommended that men be allowed to accompany their partners during childbirth. The man's growing new role as an active member in family life, and not simply a breadwinner, has been expanded by his role in assisting the birth of his children. The aim of this study was to analyze correlation of husband's support with the level of anxiety and length of labor in women giving birth.

METHODOLOGY

This cross-sectional study was conducted from May to August 2018. It included 60 pregnant women going to labor. Sampling technique was purposive sampling method. Inclusion criteria were gestational age 37 to < 42 weeks and the mother is in a normal delivery process.

Statistical Analysis: All the information was analyzed using SPSS version 23. Data were analyzed by using chi-square. $p<0.05$ was considered significant.

RESULTS

Out of 60 respondents, 28 (46.6%) were >30 years age, 41 (68.3%) had senior high school education, and the most parity status was the 2nd child (Table 1). Out of 60 respondents, 37 (61.7%) had good support during the delivery process, 25 (41.7%) respondents had anxiety levels while in labor (Table 2).

Respondents aged > 30 years had a milder level of anxiety in facing childbirth (51.1% or 22 people) compared to respondents aged < 25 years and 25-30

years. Respondents with high school education had a lighter level of anxiety in dealing with the delivery process (83.7% or 36 people) compared to respondents with elementary-high school and tertiary education.

Table 1: Characteristics of respondents.

Characteristics	Frequency (n=60)	%
Age		
- < 25 year	7	11.7
- 25-30 year	25	41.7
- > 30 year	28	46.6
Education		
- Elementary school-Junior high school	13	21.7
- Senior high school	41	68.3
- Above high school	6	10
Parity		
- Primipara	10	16.7
- Multipara 2	28	46.7
- Multipara over 2	22	36.7

Respondents with more than 2 children had a milder level of anxiety (48.8% or 21 people) compared to respondents who had 1 and 2 children (Table 3).

The statistical test results showed that there was no relationship between age and the level of anxiety in mothers giving birth at the South Tangerang Health Center in 2018 ($p=0.17$). There was a relationship between education and anxiety levels with a value of

Table 2: Research variable frequency.

Characteristics	Frequency (n=60)	%
Husband Support		
- Good	37	61.7
- Not good	23	38.7
Anxiety		
- Not worry	5	8.3
- Light	14	23.3
- Currently	25	41.7
- Heavy	9	15.0
- Very heavy	27	11.7

Table 3: Correlation between respondent characteristics and levels of anxiety in mothers.

Variable	Light		Anxiety Level Weight		Total		P value
	f (60)	%	F (60)	%	F (60)	%	
1. Age							
- < 25 year	3	7	4	23.5	7	11.7	0.17
-25-30 year	18	41.9	7	41.2	25	41.7	
- > 30 year	22	51.1	6	35.3	28	46.6	
Total	43	71.7	17	28.3	60	100	
2. Education							
- Elementary-junior high school	1	2.8	12	70.6	13	21.7	0.00
- Senior high school	36	83.7	5	29.4	41	68.3	
- College	6	14	0	0	6	10	
Total	43	71.7	17	28.3	60	100	
3. Parity							
- P1	3	7	7	41.2	10	16.7	0.01
- P2	19	44.2	9	52.9	28	46.7	
- P >2	21	48.8	1	5.9	22	36.7	
Total	43	71.7	17	28.3	60	100	

Table 4: Correlation between husband's support and anxiety level in maternity.

Variable	Baik		Dukungan Suami Kurang Baik		Total		P value
	f	%	f	%	f	%	
Tingkat Kecemasan							
- Ringan	37	100	6	26.1	43	71.7	0.00
-Berat	0	0	17	73.9	17	28.3	
Total	37	61.7	23	38.3	60	100	

$p=0.00$ and there was a relationship between parity and anxiety levels with a value of $p=0.01$ (Table 3).

We found that 37 (100%) respondents with good husband support had a mild level of anxiety compared to husbands who lacked support in the delivery process. Statistical test results showed that there was a relationship between husband's support and the level of anxiety for mothers giving birth with a value of $p=0.00$ (Table 4).

DISCUSSION

The results of statistical tests showed that there was no relationship between age and anxiety level with a p value of 0.17 in mothers giving birth at the South Tangerang Health Center in 2018. The results of this study are not in accordance with the opinion of Heriani, which states that there is a relationship between the age of pregnant women and the level of anxiety in facing the period before delivery.⁶

In mothers who are less than 20 years old, the development of the reproductive organs is immature so that complications often arise during childbirth. Meanwhile, in mothers who are more than 35 years old, regression of the body's cells, especially the endometrium, causes the process of pregnancy and childbirth to be at risk.⁶ The results of the statistical union showed that there was a relationship between education and anxiety levels with a value of $p=0.00$ for mothers giving birth. This is in accordance with the results of Heriani's research that there is a relationship between education pregnant women with anxiety levels in the face of the period before delivery.⁶ Pregnant women with primary and secondary education tend to experience more anxiety than mothers with higher education.⁶

The same opinion was expressed by Pasaribu, that the higher a person's education, the greater the opportunity to seek treatment from health workers.⁷ Conversely, the lower a person's education will cause a person to experience stress, where the stress and anxiety that occurs is due to the lack of information that person gets. Education is a basic human need that is needed for self-development and one's intellectual maturity. This intellectual maturity affects one's insight into one's thinking, both in actions that can be seen, and, in the way, decisions are made.

The level of education is also one of the factors that influence a person's perception of being more receptive to new technological ideas. The higher a person's education, the higher the quality of his knowledge and the more intellectually mature he is.⁷ The same thing was also mentioned in Arnita that there was a relationship between education level and antenatal care knowledge of 0.376 with a contribution of 14%.⁸ The results show that

the level of education is related to anxiety and the level of education is also related to knowledge of antenatal care.

The results of the statistical test showed that there was a relationship between parity and the level of anxiety with a value of $p=0.01$. This is in accordance with the results of the study showing that the results of the chi square correlation test yielded a value significant p of 0.009. The same thing is also in accordance with the results of Hutagalung's study showing that there is a relationship between age and parity with the length of labor with a value of $p=0.000$.⁹ This means that the higher and lower the parity of the mother, the higher the risk for the occurrence of long labor. Women with high parity are at risk of experiencing a long labor because the uterus is weakened in the uterine wall. Mothers with high parity are classified as multiparas or mothers who give birth to 5 life stages.

We found that there was a relationship between husband's support and the level of anxiety with a value of $p=0.00$ for mothers giving birth. The results are in accordance with those of Henderson study that there was relationship between husband's support received by the mother during labor with the anxiety level of the mother in labor.¹⁰

Research results of Nurheni also showed that there was a relationship between husband's support and the anxiety level of pregnant women in facing childbirth ($p=0.004$), which means that there is a relationship between husband's support and anxiety level of pregnant women in facing childbirth.¹¹

Husband support is needed by pregnant women to improve psychological well-being and adjustment as well as reduce stress and anxiety, maintain, and improve physical health in facing childbirth.¹¹ The companion can play a role by providing touch, entertainment, and encouragement to support the mother during labor. The mother's companion during the birth process should be someone who cares for the mother and the most important thing is the person the mother wants to accompany her during the birth process.¹⁰ Support has a positive impact is physical and emotional wellbeing. This support includes several aspects such as rubbing the mother's back, holding her hand, maintaining eye contact, the mother is accompanied by friendly people, and the mother is not going through the birthing process alone.¹¹

CONCLUSION

There was correlation between husband's support and the level of anxiety of mothers giving birth.

Author Contributions:

Conception and design: Abdullah Antaria, Vera Suzana Dewi Haris.
 Collection and assembly of data: Abdullah Antaria, Vera Suzana Dewi Haris.
 Analysis and interpretation of data: Abdullah Antaria, Vera Suzana Dewi Haris.
 Drafting of the article: Vera Suzana Dewi Haris.
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REFERENCES

1. Fathi Najafi T, Latifnejad Roudsari R, Ebrahimipour H. The best encouraging persons in labor: A content analysis of Iranian mothers' experiences of labor support. *Plos one*. 2017;12:e0179702.
2. Rohani, Reni S and Marisah. *Midwifery Care During Childbirth*. New York: Salemba Medika. 2011.
3. Depkes RI. 2012. *Health Profile of the Republic of Indonesia 2012*. (Online). Available: <http://www.depkes.go.id>. November 13, 2013.
4. Aritonang E. *Nutritional Needs of Pregnant Women*. Bogor: IPB. press. 2013.
5. Griffin K, Reeder M. *Maternity nursing (Volume 2) medical book*. Jakarta: EGC. 2011.
6. Heriani. Anxiety before delivery in terms of parity, age and level of education. *Aisyah Journal of Health Sciences*, Stikes Lampung Volume 2016.
7. Pasaribu. The Relationship between Parity and Age with the Anxiety Level of Third Trimester Pregnant Women in Dealing with Childbirth at the Sipea-Pea Health Center, Sorkam Barat District. *Research journal. STIKES Nauli Husada Sibolga*. 2014.
8. Arnita E. Correlation between Education Level of Primigravida Pregnant Women and Knowledge of Antenatal Care (ANC) Examination at BPS Srimartuti Piyungan, Bantul. 2012.
9. Hutagalung E. *Management of Diagnosis and Treatment of Anxiety Disorders*. 2007. http://www.idijakbar.com/proceedings/dinding_anxietas.htm. Retrieved 22 April 2012).
10. Henderson C. *The Concept of Midwifery (Essential Midwifery)*. Jakarta: EGC. 2006.
11. Nurheni A. *Complete Guide to Healthy Pregnancy and Birth*. Yogyakarta: Ar Group. 2008.

Comparison of blood cells in pregnant women during 7th and 9th month of pregnancy from Khairpur, Pakistan

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Objective: To determine the difference in blood cell, count in the pregnant woman during 7th and 9th month of pregnancy from Khairpur city.

Methodology: This experiment-based study was conducted at Kousar Hospital and Civil Hospital, Khairpur from July 2018 to September 2018. A total 114 pregnant females with age range 20-50 years were included in the study. The blood samples were processed for CBC test by using CBC analyser sysmax xp100 machine. The Data were analyzed using SPSS

and chi square test (single factor Anova).

Results: We found low hemoglobin level in 77 (68%) women of age between 20-35 and 37 (32%) women in the age between 36-50 out of 114 pregnant women.

Conclusion: Hemoglobin level and number of platelets were decreased in pregnant women especially in third trimester.

Keywords: Red blood cells, hemoglobin, pregnancy, Khairpur City.

INTRODUCTION

Anemia is one of the nutritional deficiencies in which hemoglobin level is <11g/dl. Anemia is more common in women of reproductive age and during pregnancy.¹ South Asian countries have 1.5 billion persons facing anemia.² Anemia increases the risk of neonatal growth retardation and reduced resistance to infection of both mother and baby. In pregnancy nutritional deficiency is most common factor.³

In the third trimester, untrained women had a better anemic ratio in contrast of trained women.⁴ Anemia is associated with increased risk of pre-term labor (28.2%), pre-eclampsia (31.2%) and maternal sepsis.⁵ Iron deficiency anemia varies in pregnant women of Karachi (64%), Lahore (73%), and Multan (76%).⁶ When hemoglobin level is between 10-10.9 g/dl it is said to be mild and when it is between 7-9.9 g/dl moderate and severe when it is less than 7 g/dl.⁷

Hemoglobin level decreases in pregnant women by the deficiency of iron which can cause high maternal mortality, inadequate growth, and impaired mental development.⁸ When a woman becomes pregnant, the demand for iron increases by 50%.^{9,10} It is commonly recognized that physiological changes in hemoglobin concentration, platelet count, and hematocrit value occur throughout a typical pregnancy.^{11,12} Therefore, it is advised that pregnant women undergo routine screening tests for anemia.¹³ The aim of this study was to determine the difference in blood cell count in the pregnant woman during 7th and 9th month of pregnancy in our city.

METHODOLOGY

This experiment-based study was conducted at Kousar Hospital and Civil Hospital, Khairpur from July 2018 to September 2018. The study was approved by the Ethics Committee of the University and all women gave an informed consent.

All the pregnant women age ranging 20 to 50 years were included in the study while non-pregnant women were excluded from the study. Blood samples were obtained at 7th month and 9th month of pregnancy. CBC Analyzer (Sysmex xp 100) were used. The women were divided into two age groups, in the first group women were of 20 to 35 years old and in the second group were 36 to 50 years old.

We used a questionnaire, which was filled in by face-to-face interviews. Sociodemographic characteristics were recorded. According to WHO classification those women who showed hemoglobin level <11.0g/dl were labelled as anemic. At this point patients were categorized into Mild (Hemoglobin 9.0-10.9 g/dl), moderate (Hemoglobin 7.0-8.9 g/dl) and severe anemic (Hemoglobin less than 7.0 g/dl).¹⁴

Statistical Analysis: The data were analyzed by using SPSS software (single way anova) to examine the significance of different variables.¹⁵

RESULTS

Majority of pregnant women were in the age group of 20-35 years old with 68% while in other age group of 36 to 50 years they were 32%.

Table 1: Statistical Analysis of data showing different variables of hemoglobin using Anova.

Groups	Count	Sum	Average	Variance		
Hb 7	114	1152.73	10.11167	1.868432		
Hb 9	114	1089.53	9.557281	1.80347		
Source of Variation	SS	df	MS	F	p-value	F crit
Between Groups	17.5186	1	17.5186	9.541976	0.00226	3.882934
Within Groups	414.9248	226	1.835951			
Total	432.4434	227				

Table 2. Statistical Analysis of data showing different variables of Platelets using Anova.

Groups	Count	Sum	Average	Variance		
Platelets 7	114	24603.51	215.8203	5246.215		
Platelets 9	114	22112.31	193.9676	6080.573		
Source of Variation	SS	Df	MS	F	p-value	F crit
Between Groups	27219.64	1	27219.64	4.806241	0.029377	3.882934
Within Groups	1279927	226	5663.394			
Total	1307147	227				

The anemic women in the third trimester of pregnancy, their hemoglobin level was less than <11 g/dl and gave birth to neonates with birth weight of 2.6kg, while normal pregnant women with hemoglobin level above >11 g/dl gave birth to heavier 3.3 kg babies (Normal birth weight) (Table 1). Table 2 shows that between 7th and 9th month of pregnancy the platelets were low.

DISCUSSION

Our study found that the percentage of anemia in pregnant women was high as observed by other researchers. In district Karak, the percentage of anemia in pregnant women was 67.6%; in some urban area of Pakistan was 90.5%.¹⁶ A study from Pakistan reported 35-40% urban and 43-47% village women aged between 15-44 year suffered from anemia, poor diet and deficient iron level was the cause of anemia during pregnancy.¹⁷

The prevalence of anemia among pregnant women in other developing countries ranges from 35% to 81%.¹⁸ In this study, we found that anemia was more common among the ladies in third trimester. Although serum ferritin is a good indicator for measuring stored iron in the body, a more accurate measurement of this would be from the bone marrow aspirate for hemosiderin.¹⁹

The patients who do not respond to iron supplements, vitamin B6 and B12 levels should be checked.²⁰ Sometimes the problem of anemia in pregnancy is

compounded by chronic inflammation. These chronic infections may include urinary tract infection, sexually transmitted infections, Helicobacter pylori infection and tuberculosis, which is highly prevalent in Pakistan. In patients with anemia during pregnancy, nearly 10% had high C-reactive protein without any deficiency of iron, folate, vitamin B-12 or vitamin A, suggesting chronic inflammation.²¹

It is suggested that the variations may be attributed to different causes of anemia and dietary differences, population differences, study design and difference in methodology used in determining hemoglobin levels.²² According to WHO classification, among 114 anemic pregnant women, the 19 (5.1%) were severely anemic. The proportion of severe anemia in this study was higher compared to similar studies in Nigeria 2014 (0.3%).²¹

CONCLUSION

Hemoglobin level and number of platelets are decreased in pregnant women, especially when they are in third trimester.

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REFERENCES

- World Health Organization. Global anemia reduction efforts among women of reproductive age: impact, achievement of targets and the way forward for optimizing efforts 2020.
- Haniff J, Das A, Onn TL, Rampal S, Sun CW, Nordim NM. Anemia in pregnancy in Malaysia: a cross-sectional survey. *Asia Pacif J Clin Nutr* 2007;16:527-36.
- Solange Augusta de SA, Willner E, Pereira TAD, de Souza VR, Boaventura GT, de Azeredo VB. Anemia in pregnancy: impact on weight and in the development of anemia in newborn. *Nutricion Hospitalaria* 2015;32:2071-9.
- Ullah I, Zahid M, Khan MI, Shah M. Prevalence of anemia in pregnant women in District Karak Khyber Pakhtunkhwa. *Pak Int J Biosci* 2013;3:77-83.
- Abbaspour N, Hurrell R, Kelishadi R. Review of iron and its importance for human health. *Journal of research in medical sciences: J Isfahan Univ Med Sci* 2014;19:164-8.
- Khan DA, Fatima S, Imran R, Khan FA. Iron, folate, and cobalamin deficiency in anaemic pregnant females in tertiary care centre at Rawalpindi. *J Ayub Med Coll Abbottabad* 2010;22:17-21.
- Parks S, Hoffman MK, Goudar SS, Patel A, Saleem S, Ali SA, et al. Maternal anemia, and maternal, fetal, and neonatal outcomes in a prospective cohort study in India and Pakistan. *Int J Obstetr Gynaecol* 2019;126:737-43.
- Di Renzo GC, Spano F, Giardina I, Brillo E, Clerici G, Roura LC. Iron deficiency anaemia in pregnancy. *Women's Health* 2015;11:891-900.
- Shiro Kozuma. Approaches to anemia in pregnancy, *JMAJ* 2009;52:214-8.
- Chowdhury S, Rahman M, Muniruddin ABM. Etiology of anemia in pregnancy. *Medicine Today* 2014;2:49-52.
- Ichipi-Ifukor PC, Jacobs J, Ichipi-Ifukor RN, Ewrhe OL. Changes in Hematological Indices in Normal Pregnancy. *Physiology J* 2013; Article ID 283814:4.
- Fay RA, Hughes AO, Farron NT. Platelets in pregnancy: Hyper destruction in pregnancy. *Obstet Gynecol* 1983;61:238-40.
- Gautam CS, Saha L, Sekhari K, Saha PK. Iron deficiency in pregnancy and the rationality of Iron supplements prescribed during pregnancy. *Medscape J Med* 2008;10:283-5.
- Manzoor M, Ahmed QA, Ahmed S, Manzoor S. Frequency and causes of iron deficiency anemia in patients visiting gynaecology unit: an institutional based study. *Punjab Univ J Zool* 2017;32:111-5.
- Manzoor F, Wei L, Hussain A, Asif M, Shah SI. Patient satisfaction with health care services; an application of physician's behavior as a moderator. *Int J Environ Res Public Health* 2019;16:3318.
- Baig-Ansari N, Badruddin SH, Karmaliani R, Harris H, Jehan I, Pasha O, et al. Goldenberg. Anemia prevalence and risk factors in pregnant women in an urban area of Pakistan. *Food Nutr Bull* 2008;29:132-9.
- Khan RS, Ain HB, Tufail T, Imran M, Imran S, Siddique R, et al. Undernutrition with Special Reference to Iron-deficiency Anemia in Reproductive Age Group Females in Pakistan: Iron-deficiency Anemia in Reproductive Age group Females. *Pak Bio Med J* 2022;5:21-8.
- Broek VN, Letky EA. Etiology of anemia in pregnancy in south Malawi. *Am J Clin Nutr* 2000;72:247-9.
- Daru J, Colman K, Stanworth SJ, De La Salle B, Wood EM, Pasricha SR. Serum ferritin as an indicator of iron status: what do we need to know? *Am J Clin Nutr* 2017;106:1634-9.
- Cheng HL, Bryant C, Cook R, O'connor H, Rooney K, Steinbeck K. The relationship between obesity and hypoferraemia in adults: a systematic review. *Obes Rev* 2012; 13:150-61.
- Olatunbosun OA, Abasiattai AM, Bassey EA, James RS, Ibanga G, Morgan A. Prevalence of anaemia among pregnant women at booking in the University of Uyo Teaching Hospital, Uyo, Nigeria. *BioMed Res Int* 2014. doi.org/10.1155/2014/849080
- Muñoz M, Peña-Rosas JP, Robinson S, Milman N, Holzgreve W, Breyman C, et al. Patient blood management in obstetrics: management of anaemia and haematinic deficiencies in pregnancy and in the post-partum period: NATA consensus statement. *Transf Med* 2018;28:22-39.

Effectiveness of metformin in recurrent miscarriages in a woman with polycystic ovarian syndrome

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Objective: To evaluate the efficacy of metformin in treatment of recurrent miscarriage in women with polycystic ovary syndrome versus a placebo.

Methodology: This randomized controlled trial was carried out at Department of Gynecology and Obstetrics, Imran Idrees Teaching Hospital, Sialkot Medical College, Sialkot from 1st January to 30th June 2023. Women were divided in two groups. One group continued oral metformin 1000-2000 mg daily up to 24th weeks with folic acid 5mg daily in first trimester act as cases and other group stopped metformin after the confirmation of pregnancy acted as control. Patients were followed to detect any pregnancy loss in two groups. Data were analyzed in SPSS 25.

Results: In metformin group, there were 26 (86.7%) cases and in control group there were 13 (43.3%) cases.

Mean age of cases in metformin group was 27.33±5.09 years and in control group 30.87±6.36 years. Mean gestational age in metformin group was 26.77±3.42 weeks and in control group it was 26.77±3.42. Effectiveness was observed in 4 (13.3%) cases in metformin group and 17 (56.7%) cases in control group the treatment was not effective. Effectiveness was significantly high in metformin group as compared to control group ($p<0.05$).

Conclusion: For non-obese women with PCOS, metformin is an ovulation induction drug having benefits over clomiphene and other standard therapies for anovulatory infertility.

Keywords: Anovulation, hirsutism, hyperandrogenism, infertility, insulin resistance, metformin, polycystic ovary syndrome.

INTRODUCTION

The most prevalent endocrine condition is polycystic ovary syndrome (PCOS). Five to ten percent of reproductive-age women have it.¹ Oligomenorrhea, hyperandrogenism, and presence of polycystic ovaries on ultrasonography are three main diagnostic criteria for PCOS.¹ It increases risk of complications such as gestational diabetes mellitus (5%-40%), hypertensive disorder of pregnancy (10-30%), premature delivery (6%-15%), or early pregnancy loss (5%),² and recurrent miscarriages.³ These women have higher risk of miscarrying (30-50%).⁴

Obesity, excessive luteinizing hormone production, insulin resistance, hyperandrogenism, and impaired endometrial receptivity have a role in pregnancy loss.³ High levels of insulin contribute to recurrent miscarriages in PCOS.⁵ It is associated with insulin resistance, hyperinsulinaemia, and reduced glucose tolerance mainly in overweight women ($BMI \geq 30$).¹ At the location of implantation, hyperinsulinaemia reduces production of glycodeclin and (insulin like growth factor binding protein 1) IGFBP1.⁵ Frequent miscarriage has been linked to chromosomal abnormalities, uterine abnormalities, autoimmune disease and endocrinological

disorders.⁶

Miscarriage rates in women with PCOS may be lowered by taking metformin throughout pregnancy due to its positive effects on free testosterone, insulin sensitivity, plasminogen activator inhibitor-1, uterine vascularity, and vascular resistance.³ It decreased miscarriage rates from 83.7% to 15.5%.⁶ It had no negative effects on the babies' height, weight, motor, or social development, hence it is not teratogenic.⁷ There is lack of locally accessible evidence on the efficacy of metformin in preventing recurrent miscarriage in women with PCOS. The purpose of our study was to determine whether or not metformin is useful in reducing the risk of miscarriage for women with PCOS.

METHODOLOGY

This randomized controlled trial was conducted at Department of Gynecology and Obstetrics, Imran Idrees Teaching Hospital, Sialkot Medical College, Sialkot from 1st January to 30th June 2023. Ethical committee of Sialkot Medical College approved the study (Ref. No. SMC/IIIRS/IRB-08 dated January 1, 2023) and an Informed written consent was taken from each patient. With the help of WHO sample size calculator, sample

size of total 60 females; 30 in both groups was estimated by keeping significance level at 5%, power of study at 90% and population proportion as 83.7% with metformin and 15.5% with placebo.⁶ Sampling method was non-probability consecutive sampling technique.

Females of age 18-40 years of age, BMI 20-25 kg/m³, previous history of recurrent miscarriages, normal serum urea and creatinine level, taking metformin 3 months preconception at the dose of 1000-2000 mg a day, gestational age more than 4-5 weeks, non-diabetic women with were enrolled in the study. Any patients with PCOS or hyperinsulinemia previously treated by any form of insulin sensitizer, antiphospholipid syndrome, intrauterine abnormalities, fibroids distorting uterine cavity, other identifiable causes of recurrent miscarriages e.g., diabetes, thyroid disease and SLE, renal impairment were excluded from study.

PCOS was defined by the presence of two out of the following three criteria (1) hyperandrogenism [clinical (acne, hirsutism, balding) and/or biochemical (mainly testosterone >0.5-3.5nmol/L)], (2) oligomenorrhea (cycle >35 days) or polycystic ovarian morphology on ultrasound (ovary with 12 or more follicles measuring 2-9 mm in diameter and/or increased ovarian volume >10 cm³).

Age, BMI, parity, number of miscarriages, sonological evidence of pregnancy loss, effectiveness, address, and contact number were recorded. All the women were divided in two groups by lottery method. One group was continued oral metformin 1000-2000 mg a day up to 24th weeks of gestation per orally with folic acid 5mg once daily in first trimester acted as cases and other group stopped metformin after the confirmation of pregnancy on ultrasound acted as control.

Patients were followed-up monthly by serial ultrasound examination to detect any pregnancy loss. Outcome was assessed as no pregnancy loss until 24 weeks of gestation and recurrent miscarriages if three or more consecutive miscarriages of clinically recognized pregnancies prior to the 24th week of gestation.

Statistical Analysis: Data were analyzed through SPSS version 25. The Chi square test was applied to compare effectiveness between two groups. $p \leq 0.05$ was considered significant.

RESULTS

The mean age of cases in metformin group was 27.33 ± 5.09 years and in control group was 30.87 ± 6.36 years. The mean BMI in metformin and control group was 22.75 ± 1.43 and 22.73 ± 1.17 . The mean parity was 5.13 ± 1.04 in metformin group and 5.40 ± 1.10 in control group. The mean number of miscarriages in metformin

group and control group was 4.13 ± 1.04 and 4.40 ± 1.10 . The mean gestational age in metformin group was 26.77 ± 3.42 weeks and control group were 26.77 ± 3.42 and 20.53 ± 7.69 (Table 1) Effectiveness of treatment was achieved in 39 (65%) cases. (Fig. 1)

Table 1: Baseline features of females in both groups (n=60).

Variable	Metformin n = 30	Control n = 30
Age (years)	27.33 ± 5.09	30.87 ± 6.36
Body mass index (kg/m ²)	22.75 ± 1.43	22.73 ± 1.17
Parity	5.13 ± 1.04	5.40 ± 1.10
Number of miscarriages	4.13 ± 1.04	4.40 ± 1.10
Gestational age (weeks)	26.77 ± 3.42	20.53 ± 7.69

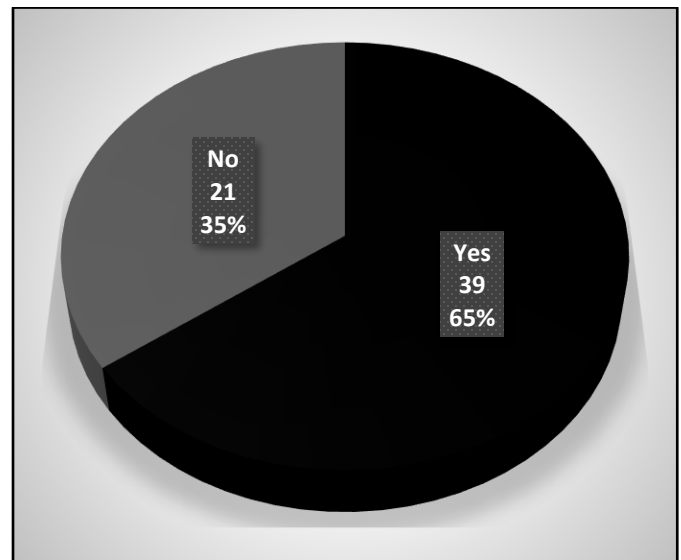


Fig. Effectiveness of treatment.

Table 2: Comparison of effectiveness in both groups.

Effective	Study Group		Total	p-value
	Metformin	Control		
Yes	26 (86.7%)	13 (43.3%)	39 (65%)	<0.001
No	4 (13.3%)	17 (56.7%)	21 (35%)	
Total	30 (100%)	30 (100%)	60 (100%)	

In metformin group, there were 26(86.7%) cases and in control group there were 13(43.3%) cases that had

effectiveness of the treatments while in 4(13.3%) cases in metformin group and 17(56.7%) cases in control group the treatment was not effectiveness. The frequency of effectiveness was significantly high in metformin group as compared to controlled group ($p < 0.05$) (Table 2).

DISCUSSION

In most women with recurrent miscarriages, underlying medical condition may be identified and treated.⁸ However, in almost half of all instances, the precise etiology is still unknown.⁹ PCOS affects 5-10% of reproductive-aged women and is the leading cause of anovulatory infertility. Women with PCOS also have a higher chance of miscarriage.¹⁰

Prevalence of early pregnancy loss (EPL) is claimed to be between 10 and 15%, the reported rate of EPL in women with PCOS is 30-50%.¹¹ Evaluation of women who had repeated miscarriages leads to a diagnosis of PCOS in 36-82% cases.¹² Live-birth rates were not increased when these women their endogenous release of LH suppressed prior to conception.¹³ Recent investigations have shown hyperinsulinemia and insulin resistance are hallmarks of PCOS, causing anovulation.¹⁴ Metformin has demonstrated to boost ovulation rates in women with PCOS.¹⁵ It enhances insulin sensitivity.¹⁶ In current study, in metformin group there were 26(86.7%) cases and in control group there were 13(43.3%) cases that had effectiveness of the treatments. The frequency of effectiveness was significantly high in metformin group as compared to controlled group ($p < 0.05$).

In a recent prospective cohort research, 106 women with PCOS who did not have diabetes and who got pregnant while using metformin participated. Early pregnancy loss was significantly lower in metformin group (8.9%; 5/56) than in control group (36%; 18/50; $p = 0.001$). There were 35 miscarriages out of 50 pregnancies in the metformin group, for a loss rate of 45%. According to the results, Metformin during pregnancy in women with PCOS significantly reduced the risk of miscarriage.¹⁷

In 2010, a local case-control study assessed the efficacy of metformin in lowering EPL in PCOS patients. Keeping on metformin throughout pregnancy was observed to lower EPL by 8.8% compared to 29.4% in control group ($p = 0.001$). Metformin reduced pregnancy loss to 12.5% compared to 49.4% in the control group ($p = 0.002$) among women who had experienced a miscarriage before. Thus, EPL was greatly reduced in women with PCOS when Metformin is continued during pregnancy indicating a possible major role for IR in EPL.⁴

Khattab et al, performed a prospective cohort study to evaluate the safety and effectiveness of metformin for eighty women with PCOS who were pregnant. The rate

of pregnancy losses was reduced by 66.7% in the metformin group compared to the control group's 36.3%.¹⁸ Metformin is the best option for treating recurrent miscarriage in women with PCOS, according to the results of the present study and previous research.

CONCLUSION

Metformin group showed its efficacy more often than the control group did. For non-obese women with PCOS, metformin is an ovulation induction drug that has certain benefits over clomiphene and other standard therapies for ovulatory infertility.

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REFERENCES

1. Kumar P, Khan K. Effects of metformin use in pregnant patients with polycystic ovary syndrome. *J Hum Reprod Sci* 2012;5:166-9.
2. Ghazeeri GS, Nassar AH, Younes Z, Awwad JT. Pregnancy outcomes and the effect of metformin treatment in women with polycystic ovary syndrome: an overview. *Acta Obstetr Gynecol Scand* 2012;91:658-78.
3. Ispasoiu C-A, Chicea R, Stamatian FV, Ispasoiu F. High fasting insulin levels and insulin resistance may be linked to idiopathic recurrent pregnancy loss: a case-control study. *Int J Endocrinol* 2013;2013:1-5.
4. Nawaz FH, Rizvi J. Continuation of metformin reduces early pregnancy loss in obese Pakistani women with polycystic ovarian syndrome. *Gynecol Obstetr Invest* 2010;69:184-9.
5. Rojas J, Chávez-Castillo M, Bermúdez V. The role of metformin in metabolic disturbances during pregnancy: polycystic ovary syndrome and gestational diabetes mellitus. *Int J Reprod Med* 2014;2014:1-15.
6. Swadi AA, Swadi SM. Effect of metformin on pregnancy outcomes in women with PCOS. *Al-Qadisiyah Med J* 2017;10:187-95.
7. Lautatzis M-E, Goulis DG, Vrontakis M. Efficacy and safety of metformin during pregnancy in women with gestational diabetes mellitus or polycystic ovary syndrome: a systematic review. *Metabolism* 2013;62:1522-34.
8. Cocksedge KA, Li T-C, Saravelos SH, Metwally M. A reappraisal of the role of polycystic ovary syndrome in

- recurrent miscarriage. *Reprod Biomed Online* 2008;17:151-60.
9. Yang CJ, Stone P, Stewart AW. The epidemiology of recurrent miscarriage: a descriptive study of 1214 prepregnant women with recurrent miscarriage. *Aust NZ J Obstet Gynaecol* 2006;46:316-22.
 10. Haq F, Rizvi J. Infertility and polycystic ovarian syndrome: A study of association between body mass index and intrafamily marriages. *Gynaecol Obstet Invest* 2008;65:269-74.
 11. Balen AH, Dresner M, Scott EM, Drife JO. Should obese women with polycystic ovary syndrome receive treatment for infertility? : *BMJ*; 2006.
 12. Ehrmann DA. Polycystic ovary syndrome. *N Engl J Med* 2005;352:1223-36.
 13. Checa M, Requena A, Salvador C, Tur R, Callejo J, Espinos J, et al. Insulin-sensitizing agents: use in pregnancy and as therapy in polycystic ovary syndrome. *Hum Reprod Update* 2005;11:375-90.
 14. Haq F, Aftab O, Rizvi J. Clinical, biochemical and ultrasonographic features of infertile women with polycystic ovarian syndrome. *J Coll Physicians Surg Pak* 2007;17:76-80.
 15. Boomsma C, Eijkemans M, Hughes E, Visser G, Fauser B, Macklon N. A meta-analysis of pregnancy outcomes in women with polycystic ovary syndrome. *Hum Reprod Update* 2006;12:673-83.
 16. Moghetti P, Castello R, Negri C, Tosi F, Perrone F, Caputo M, et al. Metformin effects on clinical features, endocrine and metabolic profiles, and insulin sensitivity in polycystic ovary syndrome: a randomized, double-blind, placebo-controlled 6-month trial, followed by open, long-term clinical evaluation. *J Clin Endocrinol Metab* 2000;85:139-46.
 17. Al-Biate MA. Effect of metformin on early pregnancy loss in women with polycystic ovary syndrome. *Taiwan J Obstet Gynecol* 2015;54:266-9.
 18. Khattab S, Mohsen IA, Foutouh IA, Ramadan A, Moaz M, Al-Inany H. Metformin reduces abortion in pregnant women with polycystic ovary syndrome. *Gynecol Endocrinol* 2006;22:680-4.

Evaluation of allergen sensitization in Pakistani patients with allergic conjunctivitis

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Objective: To evaluate the sensitization to aeroallergens in allergic conjunctivitis in Pakistani population.

Methodology: This quasi-experimental study was carried out in the Ophthalmology Department, Federal General Hospital and Allergy center, Islamabad. We enrolled 236 patients of allergic conjunctivitis which were diagnosed clinically based on a thorough history and detailed ophthalmic examination. Allergic conjunctivitis was categorized into vernal, perennial, seasonal and atopic types. All patients underwent a skin prick test.

Results: Mean age of participants was 25.05 ± 12.87 years and 63.1% were females. Vernal conjunctivitis (VKC) was the most prevalent type, present in 45.3% patients. Skin prick test (SPT) was positive in the majority of the patients (78.4%). No significant

association was found between sensitivity status of SPT versus categories (types) of allergic conjunctivitis ($p=0.658$). Most common aeroallergen was dust followed by pollen. We found that 61.5% had sensitization to more than one allergen. Allergen sensitization was not associated with different types of allergic conjunctivitis ($p=0.689$). SPT was positive more in females ($p=0.015$) and more in patients less than 40 years of age ($p=0.018$).

Conclusion: Although majority of our patients had positive results to aeroallergen skin prick test, and sensitivity to more than one allergen, no significant association was established between various types of allergic conjunctivitis and specific aeroallergens.

Keywords: Allergic conjunctivitis, vernal keratoconjunctivitis, allergens, hypersensitivity.

INTRODUCTION

Global epidemiological data shows a marked increase in prevalence of allergic illnesses in the previous few decades.¹ This rise is more noticeable in the Asian continent,²⁻⁴ leading to frequent presentation of allergic diseases in day-to-day clinical practice. Allergic conjunctivitis shows rather a variable prevalence for the general population ranging from 6%–30%,⁵ causing huge burden on health care system. Inadequate management of allergic conjunctivitis in rare cases can cause corneal complications, which eventually lead to compromised vision.⁶

Several allergens have been identified in the pathogenesis of allergic conjunctivitis. Different studies conducted worldwide have used skin prick test (SPT) to investigate allergen sensitization and reported dust and pollen among the most common allergens involved with allergic conjunctivitis.⁷⁻¹⁰ In Pakistan, the prevalence of allergic conjunctivitis is reported to be 19.2%¹¹ but there is scarcity of data available on allergens related with allergic conjunctivitis. The key emphasis of our study was to evaluate the significance of skin prick test, and allergen sensitization of such allergic conjunctivitis patients presenting in Federal General Hospital.

METHODOLOGY

This quasi-experimental study enrolled 236 patients of allergic conjunctivitis (age range 5-60 years) from Ophthalmology Department of Federal General Hospital, Islamabad from January 2021 to August 2022. It was approved by Hospital's ethical committee (Ref No. F-3-144/ADMN-EC-FGH dated 19/11/2020). Informed consent was taken from all the patients or their parents in case the patient is younger than 18 years. We calculated sample size using open Epi tool kit sample size calculator considering the prevalence of allergic conjunctivitis to be 19.2% with confidence interval of 95% and margin of error of 5%.

Patients having other types of conjunctivitis (like contact lens related conjunctivitis and infectious conjunctivitis) or ocular surface disease (like dry eyes and herpes simplex keratitis) were excluded from the study. Pregnant ladies, lactating mothers, patients with connective tissue diseases, history of severe urticaria, angioedema or previous attack of anaphylaxis, patients on systemic medications (like steroids and anti-histamines) which can affect the results of skin prick test were also excluded.

All patients had thorough slit lamp examination and a clinical diagnosis of allergic conjunctivitis was established and categorized as vernal, perennial, seasonal

and atopic taking into account history and examination. All underwent SPT at Allergy center by trained medical personnel, under supervision of a specialist allergist/dermatologist. SPT was carried out using aeroallergen extracts of five aeroallergens comprising dust, mixed pollen, pollen of paper mulberry, raw cotton and thresher dust. The mean wheal diameter (MWD) was calculated by taking an average of the two biggest dimensions through the wheal. SPT was taken as positive if the MWD was calculated to be ≥ 3 mm. In positive cases sensitization to specific antigen/aeroallergens

Table 1: Comparison of demographic features, type of allergic conjunctivitis and sensitivity to SPT (n=236).

Variables	Positive SPT n=185, (78.4%)	Negative SPT n=51, (21.6%)	p-value*
Gender:			
Male n= 87 (36.9%)	61 33%	26 51%	0.015
Female n=149 (63.1%)	124 67%	25 49%	
Age Group			
5-20y n=111 (47 %)	80 43.2%	31 60.8%	0.018
21-40y n=95 (40.3 %)	83 44.9%	12 23.5%	
41-60y n=36 (12.7 %)	22 11.9%	8 15.7%	
Type of allergic conjunctivitis:			
Seasonal n=39 (16.5%)	32 17.3%	7 13.7%	0.658
Perennial n=66 (28.0%)	54 29.2%	12 23.5%	
Vernal n=107 (45.3%)	80 43.2%	27 53%	
Atopic n= 24 (10.2%)	19 10.3%	5 9.8%	

*Chi square test

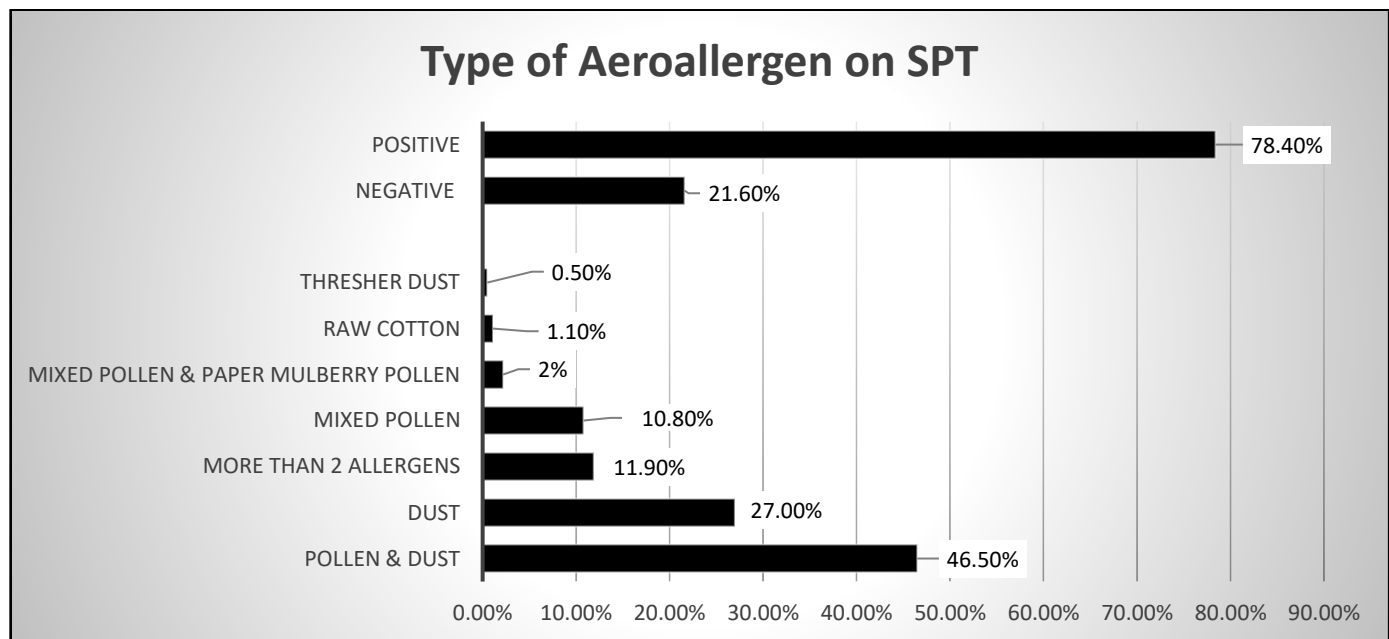


Fig. 1: Results of SPT and sensitivity to various types of aeroallergens.

and number of aeroallergens was also noted.

Statistical Analysis: Data were analyzed using SPSS version 23. The chi-square test was applied to associate skin prick test with gender, age group and type of allergic conjunctivitis. $p \leq 0.05$ was taken as significant.

RESULTS

Out of 236 patients, 87 (36.9%) were males and 149

(63.1%) females. Mean age was 25.05 ± 12.87 years. The comparison of demographic features, type of allergic conjunctivitis and sensitivity to SPT amongst study population are shown in Table 1.

There was a significant association between conjunctivitis and general age distribution of patients ($p < 0.000$). Vernal keratoconjunctivitis (VKC) was the most prevalent type of conjunctivitis presenting in

Table 2: Comparison of number of aeroallergens sensitization with types of allergic conjunctivitis (n=185).

Number of Aeroallergens	Seasonal n=32 (17.3%)	Perennial n=54 (29.2%)	Vernal n=79 (42.7%)	Atopic n=20 (10.8%)	p-value
1 Allergen 73 (39.5%)	15 (46.9%)	18 (33.3%)	32 (40.5%)	10 (50%)	0.455
2 Allergens 90 (48.6%) Pollen +dust 86(95.6%) Mixed pollen +paper mulberry pollen 4(4.4%)	14 (43.8%)	27 (50%)	39 (49.4%)	8 (40%)	
>2 Allergen 22 (11.9%)	3 (9.4%)	9 (16.7%)	8 (10.1%)	2 (10%)	

107 (45.3%) patients. Amongst patients in up to 20-year age group, 91 had VKC, ($p<0.000$).

A significant association was found for gender and younger age with SPT, which was positive more in females than males, ($p=0.015$), and in patients less than 40 years of age, ($p=0.018$) (Fig. 1). Most of the study population (112 (61.5%) patients) had sensitization to more than one allergen (Table 2).

DISCUSSION

Studies have reported the SPT positive rates in allergic conjunctivitis from 38.7%;¹³ Pakistani population with mean age 18.62 ± 8.15 years to 82% of patients in Italian population with mean age 38 ± 19 years.¹⁴ In the current study, SPT was positive in 78.4% of the study population. In a previous local study on a large sample size (65067 patients), 68.6% were SPT positive.¹⁵ In another local study, SPT was positive in 79.7% of patients.¹⁶

In a recent study on Mexican population, SPT was positive in 78.18% cases of allergic conjunctivitis.¹⁰ Similar findings were seen in Saudi population (76%),⁷ but relatively smaller percentage of positive SPT reaction was noted in Egyptian population (42.7%).⁸ In a recent meta-analysis on VKC patients, 57.7% showed sensitization to injected allergens.¹⁷ Differences in study cohort age, gender, concomitant systemic allergies, and environmental factors are responsible for these variations.

Considering that a significant proportion of patients test positive for skin prick test, SPT may prove to be beneficial in diagnosis and management of allergic conjunctivitis patients. An Egyptian study suggested that SPT should be done for patients with allergic conjunctivitis especially those who do not have collateral atopy.⁸ Ahmed A et al, also found significant association between allergic conjunctivitis and mixed pollen/thresher

dust and cotton.¹⁵ In contrast, a local research showed poor correlation of SPT with severity of allergic conjunctivitis and suggested that SPT had little utility to determine severity of disease.¹³ It is postulated that SPT can be positive in IgE mediated allergies,¹⁴ and systemic hypersensitivity.

In our study, the most prevalent aeroallergen was dust (27.0%) followed by mixed pollen (10.8%). Comparable results were seen in Saudi patients where dust was the leading allergen (43%).⁷ Dust and pollen were the main allergen in Chinese population.¹⁸ In Egyptian population dust mites and pollen was most prevalent allergen.⁸ Lebanese population showed dust mites 92% as most common allergen followed by pollen.¹⁹ Thai children had house dust mites in 86.1%,²⁰ and Pollen sensitivity was most common in Italy.¹⁴

In our study majority of study population (61.5% patients) had sensitization to more than one allergen as compared to 84% in Thai population.²⁰ Similarly in a recent survey on Mexican cohort patients and Chinese pediatric population were found to be sensitive to multiple allergens.^{10,18} The present study did not find any significant association of the distribution of allergen sensitization with different types of allergic conjunctivitis ($p=0.689$). Similar findings were noted by a study on Thai population in which allergens tested were mites, cockroaches, pollen, pets and molds.²⁰

In our study, VKC (45.3%) was the most common type of allergic conjunctivitis. Comparable findings were documented by other hospital-based studies i.e., 46.2% in Pakistani population,¹⁶ and 64% in Egyptian population.⁸ In a population-based survey on Italian population (temperate climate areas), seasonal allergic conjunctivitis was the most prevalent type of conjunctivitis (55%).¹⁴ A study from Thailand (tropical climate) reported perennial allergic conjunctivitis as most prevalent (61.6%).²⁰

The strengths of our study are that we have a large sample size including a wide range of age groups. This allowed us to study all types of allergic conjunctivitis with sufficient number to reduce examiner bias. Ophthalmic examinations in all patients were performed by a single and senior ophthalmologist. Similarly results of SPT were interpreted by a single examiner. There are few limitations to the study. First, we used a limited number of aeroallergens. International studies have used up to fourteen allergens in SPT. We did not investigate the role of concomitant systemic allergies and serum IgE levels of patients included in the study.

CONCLUSION

This study failed to document a significant association between various types of allergic conjunctivitis and specific aeroallergens. Skin prick test was tested to be positive in most of our patients and sensitivity to multiple allergens was also present commonly. Forthcoming research is required to gauge the potential outcomes of adjuvant immune therapy in SPT positive cases.

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REFERENCES

- Miyazaki D, Fukagawa K, Okamoto S, Fukushima A, Uchio E, Ebihara N, et al. Epidemiological aspects of allergic conjunctivitis. *Allergol Int* 2020;69:487-495.
- Kang SY, Song WJ, Cho SH, Chang YS. Time trends of the prevalence of allergic diseases in Korea: A systematic literature review. *Asia Pac Allergy* 2018;8:e8.
- Yu QQ, Tang J, Wang YJ, Xu YX, Liu MH. Epidemiological analysis of allergic diseases in primary and middle school students of Foshan. *Lin Chuang Er Bi Yan Hou Tou Jing Wai Ke Za Zhi*. 2019;33:970-974.
- Mehta JS, Chen WL, Cheng ACK, Cung LX, Dualan IJ, Kekunnaya R, et al. Diagnosis, Management, and Treatment of Vernal Keratoconjunctivitis in Asia: Recommendations from the Management of Vernal Keratoconjunctivitis in Asia Expert Working Group. *Front Med (Lausanne)*. 2022;9:882240. Doi: 10.3389/fmed.2022.882240.
- Thong BY. Allergic conjunctivitis in Asia. *Asia Pac Allergy* 2017;7:57-64.
- Bielory L, Delgado L, Katelaris CH, Leonardi A, Rosario N, Vichyanoud P. ICON: Diagnosis and management of allergic conjunctivitis. *Ann Allergy Asthma Immunol* 2020 ;124:118-134.
- Alqurashi KA, Bamahfouz AY, Almasoudi BM. Prevalence and causative agents of allergic conjunctivitis and its determinants in adult citizens of Western Saudi Arabia: A survey. *Oman J Ophthalmol* 2020;13:29-33.
- Abo-Ali FH, Farres MN, Shahin RY, Eissa AM, Ahmed A, Abdel-Monsef A, et al. Skin Prick Test Reactivity to Aeroallergens among Egyptian Patients with Isolated Allergic Conjunctival Disease. *Egypt J Immunol*. 2015;22:41-7.
- Gao X, Hong L, Xiang Q. A survey of allergic conjunctivitis in children in China. *Sci Rep* 12, 21026 (2022). <https://doi.org/10.1038/s41598-022-25591-7>
- Millán Martínez R, Sorcia Ramírez G, Muñoz-Pérez MJ. Sensitization to Aeroallergens in a Mexican Cohort with Allergic Conjunctivitis: A Cross-sectional Retrospective Study Conducted in Ángeles Puebla Hospital. *Ocul Immunol Inflamm* 2022;12:1-8.
- Baig R, Ali AW, Ali T, Ali A, Shah MN, Sarfaraz A, et al. Prevalence of allergic conjunctivitis in school children of Karachi. *J Pak Med Assoc* 2010;60:371-3.
- Open-Source Epidemiologic Statistics for Public Health. Available from URL: <https://www.openepi.com/SampleSize/SSPropor.htm>
- Masrur A, Adnan M, Khan FA, Tayyab A. Association of Severity of Allergic Conjunctivitis with Skin Prick Test. *J Coll Physicians Surg Pak* 2020;30:1166-9.
- Leonardi A, Piliego F, Castegnaro A, Lazzarini D, La Gloria Valerio A, Mattana P, et al. Allergic conjunctivitis: a cross-sectional study. *Clin Exp Allergy* 2015;45:1118-25.
- Ahmed A, Minhas K, Micheal S, Ahmad F. Prevalence of skin test reactivity to aeroallergens in the Pakistani population. *Public Health* 2011;125:324-6.
- Kausar A, Akhtar N, Akbar N. Epidemiological aspects of allergic conjunctivitis in Pakistani population. *J Ayub Med Coll Abbottabad* 2022;34:135-140.
- Rasmussen MLR, D'Souza M, Topal DG, Gradman J, Larsen DA, Lehrmann BB, et al. Prevalence of allergic sensitization with vernal keratoconjunctivitis: A systematic review with meta-analyses. *Acta Ophthalmol* 2023;10:9-21.
- Yang S, Jiang Y, Jin YM, Zhang JY, Li Y. Characteristics of allergic conjunctivitis with positive skin prick test. *Chin J Ophthalmol* 2017;53:689-93.
- Arej N, Irani C, Abdelmassih Y, Slim E, Antoun J, Bejjani R, et al. Evaluation of allergic sensitization in Lebanese patients with allergic conjunctivitis. *Int Ophthalmol* 2018;38:2041-2051.
- Jongvanitpak R, Vichyanond P, Jirapongsananuruk O, Visitsunthorn N, Pacham P. Clinical characteristics and outcomes of ocular allergy in Thai children. *Asian Pac J Allergy Immunol* 2022;40:407-413.
- Leonardi A, Castegnaro A, Valerio AL, Lazzarini D. Epidemiology of allergic conjunctivitis: clinical appearance and treatment patterns in a population-based study. *Curr Opin Allergy Clin Immunol* 2015;15:482-8.

Screening time induce asthenopia among screenagers of Quetta Institute of Medical Sciences, Quetta, Pakistan

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Objective: To determine frequency and association of asthenopia among screenagers of QIMS.

Methodology: This cross-sectional study was conducted at Quetta Institute of Medical Sciences from April 2023 to September 2023. Sample size of 336 was calculated by WHO calculator. Participants, who experienced any combination of three out of the nine listed symptoms, including tired eyes, headache, glare, blurred vision, backache, eye strain, sore eyes, shoulder and neck ache, and dry eyes, were identified as having asthenopia. Chi-Square test was applied to check the association between gender and screen time with Asthenopia. $p < 0.05$ was considered significant.

Results: Out of 336 participants, 274 (73.5%) were males and 89 (26.5%) females. The most common

finding was headache reported by 176 (52.4%) followed by tired eye 132 (39.3%), blurred vision 131 (39.0%), backache 127 (37.8%), neck ache 112 (33.3%), eye strain 107 (31.8%), dry eye 72 (21.4%), sore eye 50 (14.9%) and glare discomfort reported by 40 (11.9%) participants. There was a statistically significant relationship between gender ($p < 0.0001$) and screen time ($p < 0.0001$) with asthenopia.

Conclusion: Asthenopia was found among almost half of the study participants with varying degree of severity of symptoms. Association of screen hours with asthenopia was also established which was statistically significant.

Keywords: Asthenopia, tired eyes, headache, glare, blurred vision, backache, screenagers.

INTRODUCTION

The increasing use of digital technology has made devices such as laptops, computers, smartphones, and tablets widely utilized by students for both academic and social purposes.¹ As a result, students often experience asthenopia, which is a condition characterized by visual discomfort accompanied by symptoms like red or itchy eyes, dizziness, difficulty concentrating, and headaches.² The American Optometric Association (AOA) has coined the term “Computer Vision Syndrome” to describe the vision difficulties that arise from the strain put on the eyes due to prolonged use of digital screens.³ The consequences of asthenopia can significantly impact academic performance, attention span, and work capacity, thus posing a genuine concern for public health.⁴

According to the 2015 Digital Eye Strain report, approximately 90% of individuals spend more than 2-3 hours looking at screens.⁵ Clinicians often suggest taking regular breaks to reduce the impact of digital eye strain. An extensively mentioned guideline known as the 20-20-20 rule advises individuals to focus on an object that is at least 20 feet (6 m) away for duration of 20 seconds, after using digital device for 20 minutes. However, it is worth noting that there is limited scientific evidence from peer-reviewed studies that substantiates this rule.⁶

The visual problems encompass anything from simple eye strain and headaches to more specific issues like refractive errors, particularly myopia.^{7,8} Additionally, the use of high-energy violet (HEV) light in laptops screens, computer and mobile phones is believed to deeply penetrate the eyes, causing more harm to the eyes, especially the retina and leads to Acute Macular Degeneration.⁵ Not only adults, teenagers, and older children, but even preschoolers spend a significant amount of time each day watching electronic screens.⁹ Globally, there are approximately 60 million individuals affected by Digital Eye Strain, and this number grows by millions each year.¹⁰ The South Asian region, including Pakistan, has also witnessed significant technological advancements, with over 139.2 million mobile phone users reported by the Pakistan Telecommunication Authority (PTA).⁵ However, there is a lack of nationally representative data for this region. Modern teaching techniques have resulted in increased reliance on screens, thus causing emergence of a new form of students known as “Screenagers”.¹¹ The aim of this study was to determine frequency and association of asthenopia among screenagers of QIMS.

METHODOLOGY

This cross-sectional study was performed at Quetta

Institute of Medical Sciences from April 2023 to September 2023 after getting approval from IRB (Ref No. CMH QTA-IERB/17/2023). Informed consent was obtained before enrolling. Sample size of 336 was calculated using WHO calculator while keeping confidence interval at 95%, margin of error 05% and 67.8% prevalence of the asthenopia according to a recent study.² Sampling was done using a non-probability consecutive sampling technique.

Students having ≥ 18 years of age and using smartphone, laptop, and computer for one hour or more per day in the previous month were included in this study. Students having eye infection/inflammation, amblyopia, pre-existing medical ailments, conjunctivitis, retinal nerve damage, strabismus, cataract or glaucoma, high myopia (> -6.0 diopters), or history of any eye surgery were excluded from study. Participants, who experienced any combination of three out of the nine listed symptoms, including tired eyes, headache, glare, blurred vision, backache, eye strain, sore eyes, shoulder and neck ache, and dry eyes, were identified as having asthenopia.

The questionnaire was split into five sections: Demographics, Screen Time, Eye Health, Headache, and Sleep. Section 'A' collected basic demographic information of the participants, including Name (optional), Residence, Gender, Age, Education Level, Chronic diseases. Section 'B' focused on the participants' exposure to various digital devices. The section 'C' assessed the eye-related symptoms experienced by the participants during or after screen time: Recent eye disorders diagnosed, Specific symptoms experienced, Frequency of symptoms, Severity of symptoms, Duration of symptoms, Use of medication for headache. Section 'D' evaluated the occurrence and nature of headaches in

relation to screen exposure. Section 'E' explored the impact of screen time on sleep patterns.

Statistical Analysis: SPSS 23 was used for data analysis. The Chi-Square test was applied to check the association between gender and screen time with asthenopia. $p < 0.05$ was considered significant.

RESULTS

This study comprised 336 participants. Out of total, 247 (73.5%) were males with the means age of 20.21 ± 1.42 years and 89 (26.5%) were females with the mean age of 20.20 ± 1.24 years (Table 1). When the participants were inquired about the ocular symptoms the most common findings are shown in Fig. 1.

Table 1: Characteristics of the participants (n=336).

Variables		n (%)
Gender	Male	247 (73.5%)
	Female	89 (26.5%)
Use of Glasses	Yes	93 (27.7%)
	No	243 (72.3%)
H/O Eye Examination	Never	17 (5.1%)
	6 Months back	159 (47.3%)
	1 Year Back	160 (47.6%)
Screen Time	1-4 hours/day	269 (80.1%)
	>4 hours/day	67 (19.9%)

Scoring was done to find out the frequency of participants suffering from asthenopia. It was found that 182 (54.2%) were having asthenopia while 154 (45.8%) were free from it. There was a statistically significant relationship between gender ($p < 0.001$) and screen time ($p < 0.001$) with asthenopia (Table 2).

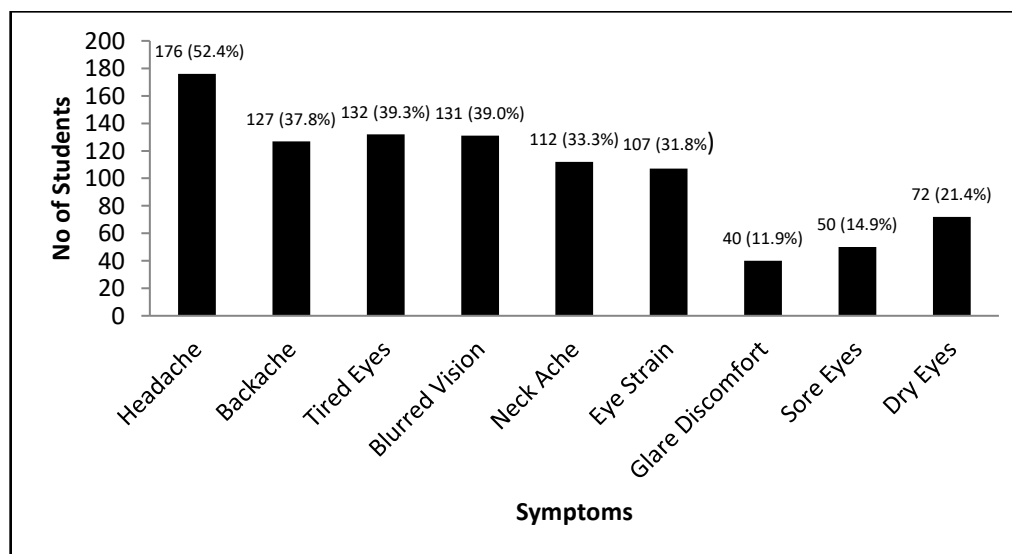


Fig. 1: Frequency of symptoms of asthenopia.

DISCUSSION

Asthenopia refers to a broad term that encompasses a range of physical or perceptual symptoms typically experienced after engaging in computer

work, reading, or other activities involving near vision.¹² Although there are conflicting reports on the causes of asthenopia, epidemiological studies have identified three primary categories of risk factors: visual problems such as refractive errors and issues with focusing;¹³ psychological factors like daily stress and poor mental well-being;¹⁴ and environmental factors including inadequate lighting, improper computer screen brightness, and prolonged periods of study. Ideally, the recommended lighting levels in a workspace range between 200 and 700 lux. According to our study, digital eye strain was present in 107(31.8%) participants which is less than 89.9% found in a study conducted in Malaysia by Reddy et al.¹⁵ Similar study was conducted by Logaraj et al,¹⁶ from India who found 78.6% while Akinbinu et al,¹⁷ found 74% of digital eye strain in their studies which is higher than our study. This percentage discrepancy is related to the research participants' age groupings, as well as their academic and professional needs.

In our study, most common symptom among the participants was headache (52.4%), which is like the study results by Maroof et al.⁵ Other studies in Iran,¹⁸ and Sri Lanka,¹⁹ also revealed that headache is the most common symptom among the asthenopia participants having 40.2% and 45.7%, respectively. Tired eyes were the second most common symptom among our participants-tired eye 132 (39.3%). Shantakumari et al,²⁰ also concluded that a tired eye is the 2nd most common symptom among screenagers which is 48%. Blurred vision was reported by 131 (39.0%) in our study while Maroof et al,⁵ reported 25% and Khalaj et al,¹⁸ reported 37% of blurred vision in their studies after continuous use of digital screens.

We found that 72 participants (21.4%) reported experiencing dry eye, while 50 participants (14.9%) reported having sore eyes. A study from UAE reported dry eyes in 22% participants and sore eyes in 38.6% participants.²⁰ The results of dry eyes were like our study, but the percentage of the sore eyes was less in our study as compared to the UAE study. The percentage of the glare discomfort was reported 40 (11.9%) in current study while a study by Moschos *et al*,²¹ reported 9.3% among the participants of New York and Maroof *et al*,⁵ reported 20.5% among the participants of Pakistan. According to our study, there was a statistically

Table 2: Relationship of various factors with asthenopia (n=336).

		Asthenopia		Total	p-value
		Yes	No		
Gender	Male	159 (64.4%)	88 (35.6%)	247 (73.5%)	<0.001
	Female	23 (25.8%)	66 (74.2%)	89 (26.5%)	
Total		182 (54.2%)	154 (45.8%)	336 (100%)	
Screen Time	1-4 hours	121 (45.0%)	148 (55.0%)	269 (80.1%)	<0.001
	>4 hours	61 (91.0%)	6 (9.0%)	67 (19.9%)	
Total		182 (54.2%)	154 (45.8%)	336 (100%)	

significant relationship between screen time and Asthenopia p value <0.001. Several factors can contribute to asthenopia, including lighting conditions, computer environments, computer screens, monitor position, computer users' posture, and computer tasks. Our study has some limitations because it includes the screenagers of the QIMS which may limit the generalizability of other population.

CONCLUSION

Asthenopia was found among almost half of the study participants with varying degree of severity of symptoms. The association of screen hours with asthenopia was also established, showing that asthenopia was significantly higher with screen use of more than 4 hours.

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REFERENCES

1. Haleem A, Javaid M, Qadri MA, Suman R. Understanding the role of digital technologies in education: A review. *Sust Oper Comp* 2022;3:275-85.
2. Sawaya RI, El Meski N, Saba JB, Lahoud C, Saab L, Haouili M, et al. Asthenopia among university students: the eye of the digital generation. *J Fam Med Prim Care* 2020;9:3921-32.
3. Alah MA, Abdeen S, Selim N, Al-Dahnaim L, Bougmiza

- I. Computer vision syndrome among students during remote learning periods: harnessing digital solutions for clear vision. *Front Public Health* 2023;11. doi.org/10.3389/fpubh.2023.1273886
4. Wang J, Zeng P, Deng XW, Liang JQ, Liao YR, Fan SX, et al. Eye habits affect the prevalence of asthenopia in patients with myopia. *J Ophthalmol* Volume 2022, Article ID 8669217, 7 pages
https://doi.org/10.1155/2022/8669217
5. Maroof S, Mashhadi SF, Azam N, Haider K, Arshad N, Zulfiqar S, et al. Relationship of screen hours with digital eye strain: a cross sectional survey from teenagers. *PAFMJ* 2019;69:182-6.
6. Johnson S, Rosenfield M. 20-20-20 Rule: Are These Numbers Justified? *Optom Vision Sci* 2023;100:52-6.
7. Li C, Cheng G, Sha T, Cheng W, Yan Y. The relationships between screen use and health indicators among infants, toddlers, and preschoolers: a meta-analysis and systematic review. *Int J Environ Res Public Health* 2020;17:7324.
8. Nakshine VS, Thute P, Khatib MN, Sarkar B. Increased screen time as a cause of declining physical, psychological health, and sleep patterns: a literary review. *Cureus* 2022;14:e30051.
9. Bassul C, Corish CA, Kearney JM. Associations between home environment, children's and parents' characteristics and children's TV screen time behavior. *Int J Environ Res Public Health* 2021;18:1589-93.
10. Zayed HA, Saied SM, Younis EA, Atlam SA. Digital eye strain: prevalence and associated factors among information technology professionals, Egypt. *Environ Sci Pollut Res* 2021;28:25187-95.
11. de Resende KM, Donato AR, Damasceno E, Gaspar JA, Junior JD, Rodrigues LS, et al. Screenagers generation: challenges and possibilities for teachers and schools. *Contribuciones a Las Ciencias Sociales* 2024;17:e4984.
12. Pillay R, Munsamy AJ. A review exploring convergence insufficiency in younger populations and e-devices in the digital era. *African Vision and Eye Health* 2021;80:12-5.
13. Wajuihian SO. Frequency of asthenopia and its association with refractive errors. *Afr Vision Eye Health* 2015;74:7-9.
14. Mocci F, Serra A, Corrias G. Psychological factors, and visual fatigue in working with video display terminals. *Occup Environ Med* 2001;58:267-9.
15. Reddy SC, Low CK, Lim YP, Low LL, Mardina F, Nursaleha MP. Computer vision syndrome: a study of knowledge and practices in university students. *Nepal J Ophthalmol* 2013;5:161-8.
16. Logaraj M, Madhupriya V, Hegde SK. Computer vision syndrome and associated factors among medical and engineering students in Chennai. *Ann Med Health Sci Res* 2014;4:179-85.
17. Akinbinu TR, Mashalla YJ. Knowledge of computer vision syndrome among computer users in the workplace in Abuja, Nigeria. 2013.
18. Khalaj M, Ebrahimi M, Shojai P, Bagherzadeh R, Sadeghi T, Ghalenoei M. Computer vision syndrome in eleven to eighteen-year-old students in Qazvin. *Biotechnol Health Sci* 2015;2:e28234.
19. Ranasinghe P, Wathurapatha WS, Perera YS, Lamabadusuriya DA, Kulatunga S, Jayawardana N, et al. Computer vision syndrome among computer office workers in a developing country: an evaluation of prevalence and risk factors. *BMC Res Notes* 2016;9:1-9.
20. Shantakumari N, Eldeeb R, Sreedharan J, Gopal K. Computer use and vision. related problems among university students in Ajman, United Arab Emirate. *Ann Med Health Sci Res* 2014;4:258-63.
21. Moschos MM, Chatziralli IP, Siasou G, Papazisis L. Visual problems in young adults due to computer use. *Klinische Monatsblätter für Augenheilkunde* 2012;229:379-81.
22. Li L, Zhang J, Chen M, Li X, Chu Q, Jiang R, et al. Contribution of total screen/online-course time to asthenopia in children during COVID-19 pandemic via influencing psychological stress. *Front Public Health* 2021;9:736617.

Oxidative stress and antioxidant Vitamin C among cataract patients: A case control study

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Objective: To compare mean of blood antioxidant Vitamin-C and oxidative stress marker (MDA) among cases of aging cataract and controls.

Methodology: This case control study was conducted at Ophthalmology Department of Bahawalpur Medical College and Teaching Hospital, Bahawalpur. There was total 40 aging cataract and 40 controls after matching age & demographics. The data were analyzed on SPSS version 27. Correlation coefficient was performed to compare mean of blood antioxidant vitamins (C) and MDA among cases of aging cataract and controls.

Results: Mean age was 61.19±5.65 years in cataract and 52.50±9.71 years in controls. In cases, mean weight was 66.42±12.86 kg and mean height was 1.65±0.08 meter. Mean waist was 93.74±14.44 cm in cataract

patients. In cases, mean of BMI was 24.25±4.93 and 21.81±4.56 in control. The weight, height, waist and BMI were higher in cases than controls. Mean random blood sugar was 112.58±34.55 mg/dl and antioxidant vitamin C was low (32.15±16.62) in cataract patients. The MDA was higher in cases than controls.

Conclusion: Serum vitamin C level is depleted among cataract. Oxidative stress MDA was significantly high in cataract patients as compared to control. Hence, oxidative stress has important initiating role in cataract formation. It highlights the importance of vitamin-C supplements to prevent age related cataract.

Keywords: Antioxidant, cataract patients, oxidative stress, Vitamin-C.

INTRODUCTION

Cataract is defined as cloudiness of transparent lens of eye and is the only cause of reversible blindness among 45% of worldwide population.¹ Cloudiness of transparent lens becomes mature after the age of 50 years.^{1,2} In Pakistan, burden of blindness is exponentially on rise since 1990 and estimated to rise till 2025.² The prevalence of age related visual impairment and blindness is 53% in Pakistan which is among top three countries after India.²

Diabetes is a major risk factor in older age, which transforms lens into completely opaque thereby interferes daily activities.³ Environmental risk factors such as ultraviolet light, smoking, genetic factors, uveitis, steroids use, surgery, trauma and some occupations may lead to cataract development.⁴ Depression, decreased productivity and poor quality of life in elderly population are also associated with cataract.⁵

Oxidative damage on aqueous humor is well established causative factor of cataract.⁶ Eye tissues are more prone to oxidative damage when free radicals are deposited due to exposure of UV light, oxygen tension and metabolic activities. The environment and pathological conditions generate reactive oxygen species (ROS), which produce oxidative damage to eye and malondialdehyde (MDA) is

marker of oxidative stress. Excess production of ROS and lower level of endogenous antioxidants leads to cataract formation. Free radical and reactive oxygen species reacts with lipid and produces peroxides, which damage the cellular structures. Lipid peroxidation product MDA is assessed in biological samples as lipid peroxidation product.⁶

Oxidative damage can be prevented by Vitamin-C (ascorbic acid), which is a vital antioxidant for vitreous humor. Vitamin-C is main antioxidant in extracellular fluid (ECF) and it is only endogenous antioxidant in ECF which completely protect lipids from peroxidative damage. It acts as co-antioxidant by generating vitamin E radicals produced during scavenging of ROS.⁷ Moreover, it acts synergistically with vitamin E to maintain the antioxidant activity of glutathione.⁸

The Vitamin-C level in serum depend upon gender, race, age, ethnicity, socioeconomic status, body mass index (BMI) and consuming supplements of Vitamin-C.¹ Estimated 3% of vitamin-C is lost every day from human body. In different populations such as Spanish Meditarrian, India & USA; there is an inverse relationship between vitamin C levels in serum & age-related cataract.⁹ A study reported association of age-related cataract with increase serum levels of Vitamin-

C.¹⁰

It is significant to reduce the burden of cataract and promote quality of life with the help of vitamin-C supplements among cataract patients of 45 to 60 years in Southern Punjab. As per the knowledge of researchers there was no reports from Southern Punjab regarding estimation of vitamin C among cataract patients till date. Hence it was deemed important to conduct a study in this region of Pakistan as to reduce the burden of visual impairment. The aim of this study was to compare blood antioxidant vitamins (C) and oxidative stress marker (MDA) among cases of ageing cataract and controls at tertiary care hospital of Southern Punjab.

METHODOLOGY

This case control study was conducted at Ophthalmology department of Bahawalpur Medical College and teaching Hospital (BMDH) Bahawalpur from October-2022 to March 2023. Ethical approval was obtained from IRB of Bahawalpur Medical College (Ref # ERC-02/2022). Written informed consent was obtained from the participants and rationale of study was well explained before enrolment and anonymity of data was also assured. The sample size was calculated by keeping an anticipated population of 100 for cases and control by standard formula of sample size $N = Z^2 * P (I-P) / d^2$. Therefore, calculated sample size was 67. the sample size was augmented as 80 for both cases and control group. The inclusion criteria were pre-diagnosed patient of cataract aged between 45 to 60 years. Through consecutive sample technique 40 patients of equal number of male & female were selected. Total 40 subjects were enrolled as a control without cataract, matched like age, socioeconomic status and gender from general population. Subjects having cataract along with the opacification or any corneal lesion, history of acute illness or chronic ocular inflammation, age related macular degeneration, had history of medication for last two weeks, having shallow anterior chamber upon anterior segment examination, any ocular pathology which prevented proper dilated examination of eye, subjects with glaucoma, any other systemic disease which affects levels of serum vitamin-C were excluded from study.

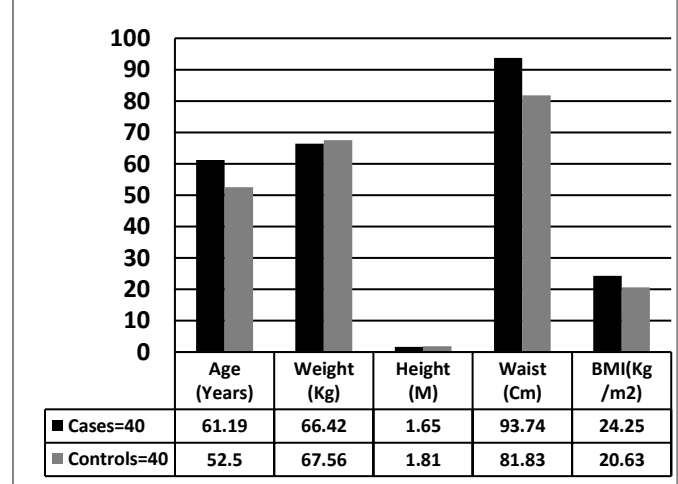
Data was collected on pre-designed proforma.¹⁻⁴ The proforma had three sections such as demographic variable age, gender and occupation. In second section, weight in kg, height in meters, waist in cm & BMI in kg/m^2 was assessed. In section three; RBS (mg/dl), malondialdehyde MDA ($\mu\text{M/L}$) and vitamin-C ($\mu\text{M/L}$) was assessed. The content validity of proforma was assessed by five senior faculty members from ophthalmology, biochemistry and medicine departments

having additional qualification in medical education. The assessment and recording of data were performed by only PI.

RBS was analyzed through lab reports of one lab for all cases and controls. Blood samples were collected in shaded room with direct sunlight. In blood, Ascorbic acid (Vitamin C) exists in an oxidized form called dehydroascorbate. Ascorbic acid and dehydroascorbate are biologically active forms. Icebox was used to store serum till enough samples were collected than transport in deep freezer at the temperature of -40°C . (DRG International USA, Ref: ENZ-4888) kit was used to analyze Vitamin-C in serum. The levels of Vitamin-C were assessed as deficient $<0.2 \text{ mg/dL}$ (11.35 mmol/L), low levels 0.2 to 0.39 mg/dL (11.35 – 22.14 mmol/L), normal level 0.4 to 0.99 mg/dL (22.71 – 56.21 mmol/L) and level $\geq 1.0 \text{ mg/dL}$ (56.78 mmol/L) indicates saturation.¹¹ DRG International USA kit was used to estimate serum MDA ($\mu\text{M/L}$) in cases & controls.

Statistical Analysis: Collected data were manually checked by PI for completeness before transferred to SPSS version 27. Shapiro-Wilk test was used to check normality of data. Correlation coefficient was performed to compare mean of blood antioxidant vitamins C and oxidative stress marker (MDA) among cases of cataract and controls. Chi square test was performed to assess association between age, weight (kg), height (meter), waist (cm) and BMI (kg/m^2). $p < 0.05$ was considered as statistically significant.

Graph-1: Comparison of demographic variables of Cases of Cataract and Controls



RESULTS

Total 40 cases and 40 controls were completed with response rate of 100%. The statistically significant association was found in age, height, weight, waist

among cases and controls (Graph-1 and Table 1). The mean of random blood sugar (RBS) was 112.58mg/dl in cases then in controls (Graph 2). Mean of vitamin-C in cataract group was lower (32.15 ± 16.62) than in control group ($p=0.001$).

The SD of RBS in cases was 34.55 measured the spread or variability of the correlation coefficient. Mean oxidative stress among cataract group was higher (3.37 ± 2.24) as compared to non-cataract at p -value of 0.001. A higher f value indicates that there was significant difference among the groups (Table 2).

DISCUSSION

This study was focused to compare vitamins-C and MDA among cases of ageing cataract and controls. In this study, mean weight was 66.42 ± 12.86 kgs in cataract patients which is lower than the study of Schuster et al, which reported the mean weight of 79.7 ± 16.6 kg in cataract patients.¹²

Mean height of cataract patients was 1.65 ± 0.08 meter and this is in congruent with the study of Schuster et al.¹² Regarding visual related quality of life among general population reported the mean height of 1.71 meter in cataract patients which is close to the findings of present study.

Mean waist among cataract cases was 93.74 ± 14.44 cm, which is in agreement with the result of Schuster et al,¹² having mean waist of 94.3 ± 13.9 cm in cataract patients.

A Meta-analysis¹³ revealed the relationship between obesity and incidence of cataract. Mean BMI was 24.25 ± 4.95 in cataract and 20.63 ± 4.87 in controls in present study. These findings were comparable with study of Layana et al and observed higher BMI in

Graph-2: Comparison of Blood Antioxidant Vitamin-C and Oxidative Stress Marker (MDA) among Cataract and Controls.

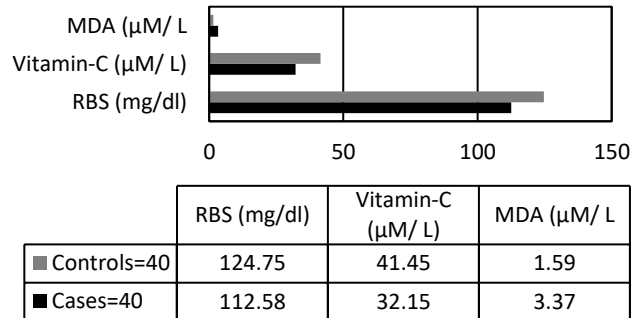


Table 1: Comparison of demographic variables among cataract (n=40) and controls (n=40)

Demographic variables		Mean	SD	95% CI		F-Value	p-Value
				Lower Boundary	Upper Boundary		
Age (Years)	Cases	61.19	5.65	49.39	55.60	12.54	0.001*
	Controls	52.50	9.71	59.44	62.92		
Weight (Kg)	Cases	66.42	12.86	63.09	70.95	0.122	0.885
	Controls	67.56	11.90	63.84	71.45		
Height (Meter)	Cases	1.65	0.08	1.63	1.84	31.04	0.001
	Controls	1.81	0.11	1.77	1.84		
Waist (cm)	Cases	93.74	14.44	89.67	98.69	15.106	0.001
	Controls	81.83	14.63	77.14	86.50		
BMI (Kg/m ²)	Cases	24.25	4.95	22.86	25.92	11.60	0.001
	Controls	20.63	4.87	19.06	22.18		
p<0.005 is statistically significant							

Table 2: Correlation Coefficient of Cataract (n=40) and control (n=40)

Variables		Mean	SD	95% CI		F-Value	p-Value
				Lower Boundary	Upper Boundary		
RBS (mg/dl)	Cases	112.58	34.55	101.88	123.18	20.297	0.001*
	Controls	124.75	9.47	121.72	127.77		
Vitamin-C µM/ L	Cases	32.15	16.62	27.59	37.86	10.64	0.001*
	Controls	41.45	9.71	38.34	44.55		
MDA µM/ L	Cases	3.37	2.24	2.63	4.00	12.642	0.001*
	Controls	1.59	0.44	1.44	1.72		
p<0.005 is statistically significant							

in cataract patients.¹⁴ Obesity is one of the risk factors of diabetes. The raised BMI in cataract patient is directly related to diabetes.¹⁵ The posterior sub capsular cataracts (PSC) are strongly associated with obesity.¹² Mean RBS was 112.58 ± 34.55 mg/dl in cataract patients and this result is in agreement with Ishaq et al.¹⁶

Mean value of vitamin-C in cataract group was lower (32.15 ± 16.62) than in control group at p-value of 0.001 in this study. This is comparable with various similar studies conducted in low income populations such as India¹⁷ and Nigeria.¹ According to a study from Southern India, vitamin-C levels in serum were found to be lower among the group having significant lens opacity than the group having no lens opacity.¹⁸ A study in Iranian population depicted no inverse relationship between cataract and vitamin-C by Abbaszadeh et al.¹⁹ It is evident that supplementary Vitamin-C has preventive and protective effect against cataract.¹

Mean MDA level among cataract group was higher (3.37 ± 2.24) as compared to non-cataract at p-value of 0.001, which is congruent with the study of Lesiewska et al.²⁰ Increased level of MDA in diabetic patients having cataract is evident from the study of Cvitkovic et al.²¹ The MDA levels among different types of age-related cataract had shown no significant difference. Hence, it is apparent that oxidative stress is initiating factor in the development of all types of cataracts.²²

It was the first ever study conducted in region of Southern Punjab to estimate MDA and Vitamin-C levels among cataract patients and indeed was the strength of study. Hospital based study and sample size was the limitation of study. It is recommended that future studies be conducted to assess cataract formation in diabetic and non-diabetic patients, levels of vitamin A and E, occupation, socio-economic level and educational level.

CONCLUSION

It was inferred from the study that serum vitamin C level is depleted among cataract. Oxidative stress MDA is significantly high in cataract patients as compared to control. Hence oxidative stress has important initiating role in cataract formation. It highlights the importance of vitamin-C supplements to prevent age related cataract.

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REFERENCES

1. Kalambe AS, Muhammad RC, Ayanniyi AA, Imam A. Serum levels of vitamin C among patients with and without age-related cataract at the University of Abuja Teaching Hospital, Abuja, Nigeria. *Nigerian J Ophthalmol.* 2022;30(2):69-74.
2. Ahsan S, Memon MS, Bukhari S, Mahmood T, Fahim MF, Haseeb U, et al. Visual outcomes of cataract surgery: An observational study of ten years from a tertiary eye care hospital in Pakistan. *Pak J Med Sci.* 2021;37(7):1775.
3. Xu J, Fu Q, Chen X, Yao K. Advances in pharmacotherapy of cataracts. *Ann Translational Med* 2020;8:1552–1552.
4. Flaxman SR, Bournee RAA, Resnikoff S, Ackland P, Braithwaite T, Cecinelli MV, et al. Global causes of blindness and distance vision impairment 1990- 2020: a systematic review and metaanalysis. *The Lancet Global Health* 2017;5: e1221–34.
5. Mailu EW, Virendrakumar B, Bechange S, Jolley E, Schmidt E. Factors associated with the uptake of cataract surgery and interventions to improve uptake in low-and middle-income countries: A systematic review. *Plos one.* 2020;15(7):5-18.
6. Tsao YT, Wu WC, Chen KJ, Liu CF, Hsueh YJ, Cheng CM, et al. An assessment of cataract severity based on antioxidant status and ascorbic acid levels in aqueous humor. *Antioxidants.* 2022;11(2):397.
7. Tram NK, McLean RM, Swindle-Reilly KE. Glutathione improves the antioxidant activity of vitamin C in human lens and retinal epithelial cells: implications for vitreous substitutes. *Curr Eye Res.* 2021;46(4):470-81.
8. Braakhuis AJ, Donaldson CI, Lim JC, Donaldson PJ. Nutritional strategies to prevent lens cataract: current status and future strategies. *Nutrients.* 2019; 11(5):1186.
9. Powers CD, Sternberg MR, Patel SB, Pfeiffer CM, Storandt RJ, Schleicher RL. Vitamin C status of US adults assessed as part of the National Health and Nutrition Examination Survey remained unchanged between 2003–2006 and 2017–2018. *J Appl Laboratory Med.* 2023;8(2):272-84.
10. Falkowska M, Młynarczyk M, Micun Z, Konopińska J, Socha K. Influence of Diet, Dietary Products and Vitamins

- on Age-Related Cataract Incidence: A Systematic Review. *Nutrients*. 2023;15(21):4585.
11. Carr AC, Rowe S. Factors affecting vitamin C status and prevalence of deficiency: A global health perspective. *Nutrients*. 2020; 12(7):1963-7.
 12. Schuster AK, Pfeiffer N, Schulz A, Nickels S, Höhn R, Wild PS, et al. The impact of pseudophakia on vision-related quality of life in the general population—The Gutenberg Health Study. *Aging (Albany NY)*. 2017;9(3):1030-1040.
 13. Ng Yin Ling C, Lim SC, Jonas JB, Sabanayagam C. Obesity and risk of age-related eye diseases: A systematic review of prospective population-based studies. *Int J Obesity*. 2021;45(9):1863-85.
 14. García-Layana A, Ciufo G, Toledo E, Martínez-González MA, Corella D, Fitó M, et al. The effect of a Mediterranean diet on the incidence of cataract surgery. *Nutrients*. 2017;9(5):453.
 15. Lim JC, Caballero Arredondo M, Braakhuis AJ, Donaldson PJ. Vitamin C and the lens: New insights into delaying the onset of cataract. *Nutrients*. 2020;12(10):3142.
 16. Ishaq H, Ali M, Kazmi N, Naqvi BS, Shaikh D. Prevalence of diabetic retinopathy in type II diabetic patients in a health facility in Karachi, Pakistan. *Trop J Pharmaceut Res*. 2016; 15(5):1069-76.
 17. Kamath Y, Bhat SS, Iqbal S, Rao LS. The association of age-related cataract and serum vitamin C. *Indian J Clin Exp Ophthalmol*. 2017; 3:287-90.
 18. Kalambe AS, Muhammad RC, Ayanniyi AA, Imam A. Serum levels of vitamin C among patients with and without age-related cataract at the University of Abuja Teaching Hospital, Abuja, Nigeria. *Nigerian J Ophthalmol*. 2022; 30(2):69-74.
 19. Choi JH, Lee E, Heo YR. The Association between dietary vitamin A and C intakes and cataract: Data from Korea National Health and Nutrition Examination Survey 2012. *Clin Nutri Res*. 2020;9(3):163-7.
 20. Lesiewska H, Woźniak A, Reisner P, Czosnyka K, Stachura J, Malukiewicz G. Is Cataract in Patients under 60 Years Associated with Oxidative Stress? *Biomedicines*. 2023;11(5):1286-9.
 21. Cvitkovic K, Sesar A, Sesar I, Pusic-Sesar A, Pejic R, Kelava T, et al. Concentrations of selected cytokines and vascular endothelial growth factor in aqueous humor and serum of diabetic patients. *Sem Ophthalmol*. 2020;35(2):126-133.
 22. Sideri O, Tsaousis KT, Li HJ, Viskadouraki M, Tsinopoulos IT. The potential role of nutrition on lens pathology: a systematic review and meta-analysis. *Survey of Ophthalmol*. 2019;64(5):668-78.

Comparison of intraocular pressure and cup disc ratio in high myope and high hyperope

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Objective: To compare and correlate intraocular pressure (IOP) and cup-to-disc (CD) ratio with high myopes and high hyperopes.

Methodology: This cross-sectional comparative study included 90 subjects visiting Riphah eye clinic, QIE campus, Lahore from Nov-22 to Oct-23. The subjects were divided into three groups: emmetropes (n=30), high hyperopes (n=30), and high myopes (n=20). Those with any ocular disorder other than refractive error were excluded. The IOP was measured by using a Goldmann applanation tonometer and cup-to-disc ratio was measured using an ophthalmoscope. The comparison and correlation of data were done using independent sample Kruskal Wallis test and Pearson correlation test.

Results: The mean IOP of emmetropes, hyperopes,

and myopes was 12.4±0.84 mm Hg, 13.83±4.01 mm Hg, and 13.43±2.06 mm Hg, respectively (p=0.377). Mean CD ratio of emmetropes, hyperopes, and myopes was 0.25±0.05, 0.31±0.14, and 0.36±0.13, respectively (p=0.011). The IOP strongly correlated positively with CD ratio (r=0.779) and age (r=0.705). Likewise, CD ratio had a strong positive correlation with age.

Conclusion: There was a non-significant difference in IOP among emmetropes, myopes, and hyperopes. Moreover, myopes had a significantly sizeable CD ratio compared to emmetropes and hyperopes. The CD ratio was large in older subjects and positively correlated with IOP.

Keywords: Myopia, hyperopia, intraocular pressure.

INTRODUCTION

There is an association between intraocular pressure (IOP) and refractive error in children, young adults, and presbyopic adults. The average IOP in a normal population is about 16±2.5 mmHg.^{1,2} IOP has also long been hypothesized as a mechanism for developing myopia or shortsightedness.³ High myopia, which is defined as the refractive error of more than -6D or at least -5D,⁴ is considered to be one of the leading causes of blindness, and its prevalence is increasing rapidly (1.6 billion people worldwide).^{3,5}

High hyperopia (longsightedness) is a refractive error characterized by a spherical equivalent of +6D or more. High myopia results in various funduscopic changes in the posterior fundus and peripheral also, and increases the risk of pathologic myopia, which may cause irreversible vision loss such as glaucoma, specifically open-angle glaucoma, retinal detachment, and macular degeneration.^{6,7} Accommodation, caused by the contraction of ciliary muscles, exerts pressure against the inner walls of the eye, which causes elongation. In contrast, continuous near work causes extraocular muscle contraction, elevating IOP.

All the previous studies mainly focused on the association of IOP with mild, moderate, and high myopia. However, Wong et al have reported an association of

hyperopia with primary angle-closure glaucoma.⁸ The optic disc is significantly smaller in hyperopic eyes with a refractive error of more than +2 D. The disc is significantly larger in highly myopic eyes.⁹ Hyperopia is mainly associated with visual system development, daily routine work, and visual functions of a child.¹⁰ This study aimed to compare IOP and CD ratios between high myopes and high hyperopes and to identify factors that may influence these measurements to distinguish normal IOP and CD ratios in different refractive errors and differentiate them from glaucoma.

METHODOLOGY

This cross-sectional comparative study included 45 subjects (90 eyes) visiting Riphah eye clinic, QIE campus, Lahore. The ethical approval was taken from the Riphah ethical review committee (REC/RCR & AHS/22/16). The consent was taken by the guardian/parent of the patient with an age below 18 years. The subjects were divided into three groups: emmetropic, hyperopic, and myopic; each group contained 30 subjects. Patients with ocular pathology like pterygium, conjunctivitis, close angle, those with any ocular surgery or systemic disease like diabetes, hypertension, or any condition affecting visual refractive status like thyroid eye disease or sarcoidosis were excluded. Subjects with

low to moderate refractive errors (less than $\pm 5D$) were also excluded.

The visual acuity was measured using the Snellen visual acuity chart. Visual acuity equal to or less than 6/9 on Snellen visual acuity chart was considered emmetropic.

The screening of subjects was done by using a slit lamp. Refraction was done objectively (autorefractometer) and subjectively. The IOP was measured by using a Goldmann applanation tonometer¹¹ and CD ratio was measured using a direct ophthalmoscope and cross-checked using a slit lamp with the help of Volks lens 90D.

Statistical Analysis:

The data were analyzed using SPSS version 23. The normality of data was assessed by using the Shapiro-Wilk test. The non-parametric test was applied to the variable with significant p-value. An independent sample Kruskal Wallis test was applied to compare variables between groups, and the correlation of variables was done using the Pearson correlation test. A Pearson correlation value of more than 0.7 was considered a good correlation. $p < 0.05$ was considered significant.

RESULTS

Age and gender details are shown in Table 1. Mean IOP of emmetropes, hyperopes, and myopes was 12.4 ± 0.84 mm Hg, 13.83 ± 4.01 mm Hg, and 13.43 ± 2.06 mm Hg, respectively ($p = 0.377$). CD was recorded higher in myopic patients than in hyperopic and emmetropes (Table 2).

The IOP strongly correlated positively with CD ratio and age and CD ratio had a strong positive correlation with age (Table 3). The R^2 of the correlation between IOP and refractive errors (spherical equivalence) was not poor; for

Table 1: Age-gender and S.E-gender distribution.

Category			N	Minimum	Maximum	Mean	SD
Age	Emmetropia	Female	12	11	44	17.6	6.731
		Male	18	18	31	23.4	6.189
	Hyperopia	Female	16	11	50	28	13.023
		Male	14	10	45	23.57	12.525
	Myopia	Female	14	11	49	28.57	12.145
		Male	16	11	46	29.31	11.388
S. E	Hyperopia	Female	16	5.50	9.00	6.55	1.65
		Male	14	5.25	12.00	7.00	3.78
	Myopia	Female	14	-9.00	-5.00	-5.79	1.24
		Male	16	-8.00	-5.00	-5.97	1.18

Table 2: IOP and CD ratio among emmetropes, hyperopes, and myopes.

Group		N	Minimum	Maximum	Mean	SD	p value
IOP	Emmetropia	30	11	13	12.40	0.84	0.38
	Hyperopia	30	11	30	13.83	4.01	
	Myopia	30	10	18	13.43	2.06	
CD Ratio	Emmetropia	30	.2	.3	.25	.05	0.011
	Hyperopia	30	.1	.8	.31	.14	
	Myopia	30	.2	.7	.36	.13	

the hyperopic eye, it was 0.010, and for myopic, it was 0.015. (Fig. 1).

Table 3: Correlation between IOP, age, and CD ratio.

	CD	Age
IOP	.779**	.705**
CD	1	.700**

**Correlation is significant at the 0.01 level (2-tailed).

DISCUSSION

A raised IOP has been observed in high myopes compared to low or moderate myopes.¹² Hence, an accurate measurement of IOP is critical in diagnosing certain diseases like glaucoma and in follow-up cases to assess the progression; even the difference of 1 mm Hg could be helpful for exact diagnosis.¹³ In literature, it is found that myopia was an independent risk factor for high IOP.

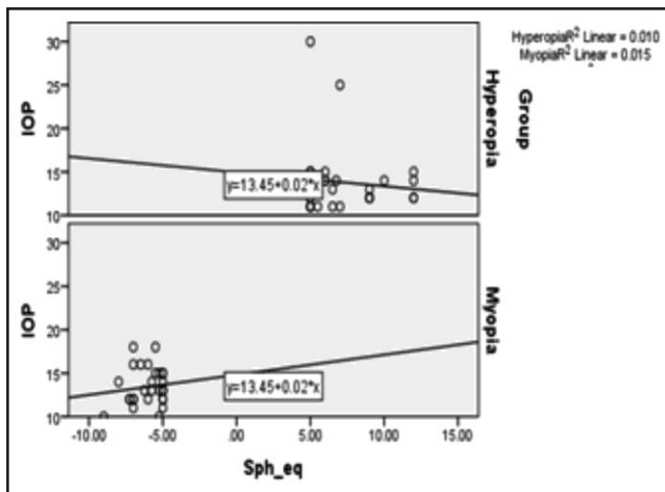


Fig. 1: Scatter chart of spherical equivalence to IOP (R2: Hypermetropia: 0.010; Myopia: 0.015).

A study by Dandan et al found a negative correlation between refractive error and IOP.¹⁴ However, current study found a raised IOP in high myopic subjects (Table 3). Two of the hyperopic group participants with the spherical equivalent of +5.50 D showed more than 25 mmHg IOP. Their fundus was normal. No ONH changes were detected. For further investigations, both subjects were referred to OCT. This finding is similar to observations made by Joseph et al¹⁵ and Mathapathi et al.¹⁶

A study has shown a decrease in axial eye length with lowered IOP and increase in AL with increased IOP.¹⁷ There are multiple theories regarding raised IOP in myopes. One theory states the cause behind raised IOP is related to the elongation of the scleral fiber wall caused by the increase of the ocular axis, which reflects the increase of intraocular pressure; it may also be related to the obstruction of aqueous humor circulation due to the structural changes of the trabecular meshwork.¹² Shen et al showed that there were 60% more chances of developing glaucoma in myopic patients as compared to emmetropic patients.¹⁸

Besides high myopia, increased corneal thickness is also a parameter that affects IOP.¹⁹ Tayyab et al found a decrease of 0.12 μ m in CCT per year. Besides IOP, a CD ratio is another important parameter in monitoring the progression of certain ocular diseases especially glaucoma.⁹ Theoretically, it is believed that the persistent rise in IOP in myopic eyes played a crucial role in the damage of the delicate optic nerve of the myopes.²⁰ Thus, besides IOP, the CD ratio is another parameter to diagnose glaucoma.

Ahn et al, found myopic shift in the large CDR group (-1.81 ± 1.71 D) was more significant than the control group (-1.47 ± 2.08 D).²¹ This study also found similar CD ratio

results in high myopes compared to high hyperopes and emmetropes (Table 2). In a glaucomatous eye, a large cup is present, but it is not only present in a glaucomatous eye; a healthy eye may also have a large cup.²²

This study found a larger CD ratio and IOP in high myopes. Moreover, there was a positive correlation between both parameters with age (Table 3). A study found a smaller cup in the hypermetropic eye, whereas a larger cup was observed in the myopic eye.²³ Further study is needed to distinguish non-tension glaucoma, like high myopia, from all other glaucoma. Central corneal thickness is another parameter that plays a crucial role in defining IOP.

CONCLUSION

High myopes and high hyperopes showed statistically no significant difference in intraocular pressure. However, a notable difference was observed in the cup-to-disc ratio, with high myopes having a significantly higher percentage than emmetropes and high hyperopes. Additionally, age exhibited a strong positive correlation with both IOP and cup-to-disc ratio, highlighting the importance of age-related considerations in assessing these ocular parameters.

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REFERENCES

1. Han X, Yang T, Zhang J, Yu S, Guo X, Yan W, et al. Longitudinal changes in intraocular pressure and association with systemic factors and refractive error: Lingtong Eye Cohort Study. *BMJ open* 2018;8:e019416.
2. Yassin SA, Al-Tamimi ER. Age, gender, and refractive error association with intraocular pressure in healthy Saudi participants: A cross-sectional study. *Saudi J Ophthalmol* 2016;30:44-8.
3. Zhang D, Wang L, Jin L, Wen Y, Zhang X, Zhang L, et al. A review of intraocular pressure (IOP) and axial myopia. *J Ophthalmol* 2022;2022.
4. Chua SY, Sabanayagam C, Cheung YB, Chia A, Valenzuela RK, Tan D, et al. Age of onset of myopia predicts risk of high myopia in later childhood in myopic Singapore children. *Ophthalmol* 2016;36:388-94.

5. Kang MT, Li SM, Li H, Li L, Li SY, Zhu BD, et al. Peripapillary retinal nerve fibre layer thickness and its association with refractive error in Chinese children: the Anyang Childhood Eye Study. *Clin Exp Ophthalmol* 2016;44:701-9.
6. Mori K, Kurihara T, Uchino M, Torii H, Kawashima M, Sasaki M, et al. High myopia and its associated factors in JPHC-NEXT eye study: a cross-sectional observational study. *J Clin Med* 2019;8:1788-90.
7. Goldschmidt E, Jacobsen N. Genetic and environmental effects on myopia development and progression. *Eye* 2014;28:126-33.
8. Wong TY, Klein BE, Klein R, Knudtson M, Lee KE. Refractive errors, intraocular pressure, and glaucoma in a white population. *Ophthalmology* 2003;110:211-7.
9. Wang YX, Panda-Jonas S, Jonas JB. Optic nerve head anatomy in myopia and glaucoma, including parapapillary zones alpha, beta, gamma and delta: histology and clinical features. *Prog Retin Eye Res* 2021;83:100933.
10. Jiang X, Tarczy-Hornoch K, Stram D, Katz J, Friedman DS, Tielsch JM, et al. Prevalence, characteristics, and risk factors of moderate or high hyperopia among multiethnic children 6 to 72 months of age: a pooled analysis of individual participant data. *Ophthalmology* 2019;126:989-99.
11. Stoor K, Karvonen E, Ohtonen P, Liinamaa MJ, Saarela V. Icare versus Goldmann in a randomised middle-aged population: The influence of central corneal thickness and refractive errors. *Eur J Ophthalmol* 2021;31:1231-9.
12. Yingying N, Xiaoxiao W, Xunlang Z, Chih-Huang Y, Yufeng S, Junguo D. Effect and correlation of intraocular pressure on the refractive status of children and adolescents. *MedRxiv* 2023;21:23290157.
13. De Bernardo M, Cembalo G, Rosa N. Reliability of intraocular pressure measurement by Goldmann applanation tonometry after refractive surgery: a review of different correction formulas. *Clin Ophthalmol* 2020;2783-8.
14. Ma D, Wei S, Sun Y, Li S-M, An W-Z, Hu J-P, et al. Distribution of IOP and its relationship with refractive error and other factors: the Anyang University Students Eye Study. *Int J Ophthalmol* 2021;14:554.
15. Joseph DS, Thampi B, Joosadima A, Mohan A. A study on the association between intraocular pressure and myopia. *Int J Res Med Sci* 2016;4:2202-5.
16. Mathapathi RS, Patil SS, Mathapathi RS. Association of refractive errors with intraocular pressure and its relationship with age and gender. *Indian J Clin Anat Physiol* 2016;3:419-22.
17. Chakraborty R, Read SA, Collins MJ. Diurnal variations in axial length, choroidal thickness, intraocular pressure, and ocular biometrics. *Investig Ophthalmol Visual Sci* 2011;52:5121-9.
18. Shen L, Melles RB, Metlapally R, Barcellos L, Schaefer C, Risch N, et al. The association of refractive error with glaucoma in a multiethnic population. *Ophthalmology* 2016;123:92-101.
19. Hashmani N, Hashmani S, Hanfi AN, Ayub M, Saad CM, Rajani H, et al. Effect of age, sex, and refractive errors on central corneal thickness measured by Oculus Pentacam®. *Clin Ophthalmol* 2017;1233-8.
20. Osaiyuwu AB, Edokpa GD. A comparative study of intraocular pressure in myopia and hyperopia among a Nigerian population just diagnosed with primary open angle glaucoma in Benin City. *Int J Res Med Sci* 2018;6:2234-7.
21. Ahn YJ, Park YY, Park SH, Shin SY. Long term change of the optic disc and OCT parameters during myopic shift in children with large cup to disc ratio. *Plos one* 2020;15:e0235621.
22. Kim YJ, Kim JM, Shim SH, Bae JH, Park KH. Associations between optic cup-to-disc ratio and systemic factors in the healthy Korean population. *Korean J Ophthalmol* 2015;29:336-43.
23. Hayreh SS, Zimmerman MB. Nonarteritic anterior ischemic optic neuropathy: refractive error and its relationship to cup/disc ratio. *Ophthalmology* 2008;115:2275-81.

Risk factors for keratoconus in Pakistani population: A case control study

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Objective: To assess the risk factors for keratoconus in Pakistani population.

Methodology: Controls were those patients who presented to outpatient department for refraction only. Controls were evaluated by an ophthalmologist and was declared as having no signs of keratoconus. Controls was age and sex matched. A pre-designed, pre-tested questionnaire was used. Questionnaire was in English language. The questionnaire covers risk factors including ocular allergies, local and systemic diseases. All the information was entered into SPSS 20.

Results: A total of 60 sample sizes were used out of which 30 were keratoconus patients and 30 were

general patients presenting Eye OPD. Data of 30 patients were taken having keratoconus and 30 controls were compared with them with corneal scarring/opacity as a risk factor.

Conclusion: Ocular allergy, which proved to be the most potent factor as it is featured with vigorous rubbing of eye, corneal scarring is also related to eye rubbing followed by inflammations of the cornea while asthma was associated with breathing problems and consequently sleeping disorders.

Keywords: Risk factors, keratoconus, Keratoconus, corneal ectasia.

INTRODUCTION

Keratoconus is a word which is derived from Greek origin where “kerato” means cornea and ‘Konos’ means cone shaped hence it is a cone shaped bulging out of the cornea. It is a non-inflammatory steepening and thinning of cornea which progresses with time.¹ Many of the sufferers of keratoconus patients chafe eyes markedly. Thus, rubbing of the eye is viewed as the prevailing causal feature in 66% of keratoconic patients who advance to hard lenses.² Keratoconus is a corneal disorder in which beneficial and investigative technologies are rising. However, its pathogenesis is still diverse and indefinable. Epidemiological vulnerability factors include ethnicity, age, gender, family record history, and rubbing of the eye. Hereditary causal factors include atopy, VKC, and DS etc.³

Keratoconus is a non-vascular axial corneal ectasia, with uncertain cause and progression. It has an incidence of 50-230 per 100,000 and is a bilateral disease in up to 90% of cases. The treatment depends on the severances of the irregular astigmatism.⁴ Family records of keratoconus have been found to be very diverse and a high incidence of keratoconus in a sample population can change the stated rate of a positive family history. Keratoconus affects both genders; a higher occurrence of keratoconus is thought to be found in patients with eye rubbing associated with ocular allergies, Down's syndrome, and retinal degenerations in a higher number.⁵ Keratoconus and other associated diseases are distinguished by

diminished and hazy visual acuity. The cause and risk factors of these diseases are unidentified however could be related to a diversity of reasons, including DS, rubbing, and itching of eye, connective tissue disease and inheritance.⁶

Standard histological features include thinning of corneal stroma and rupture in Bowman's layer. Keratoconus is generally a secluded disorder, even though several reports depict a connection with Down syndrome and mitral valve prolapse.⁷ Conversely, all disseminations were regular to the assumption that allergy and eye chafing are related in the disease producing mechanism of keratoconus merely as soon as the peak levels of these features are present. This emerge to be a sign for the necessity to progress the treatment of eye chafing for keratoconus individuals.⁸ A variety of theories have been engaged to deal with the distance in our perception of this multifaceted disorder, with the probability that with passage of time more refined remedies could be formulated.⁹ Keratoconus patients have amplified slackness to their eyelids, along with a rubberier tarsus. The high frequency of OSA in such patients is an important connection that carts an elevated risk of from any reason and stroke.¹⁰

METHODOLOGY

Patients were recruited from the outpatient department, fulfilling the inclusion criteria. A written informed consent was taken. Controls were those patients who

presented to outpatient department for refraction only. Controls were evaluated by an ophthalmologist and was declared as having no signs of keratoconus. Controls was age and sex matched. A pre-designed, pre-tested questionnaire was used. Questionnaire was in English language. The questionnaire covers risk factors including ocular allergies, local and systemic diseases. These risk factors were included in the questionnaire after extensive literature search and discussion with subject specialist. All risk factors were documented from the history and medical record of the participants. Interviews were conducted by the members trained for this purpose. All questions were asked in local language which was converted to English language by the interviewer. The interview took approximately 15 minutes.

Statistical Analysis: All the information was entered into SPSS 20 and was analyzed through its statistical package. Quantitative variables like age were presented as mean $\pm$ SD. while qualitative variables like gender were presented as frequency and percentages. A comparison of two groups of keratoconus and non-keratoconus individuals was done and we were applying chi-square. P value ≤ 0.05 will be taken as significant.

RESULTS

A total of 60 sample sizes were used out of which 30 were keratoconus patients and 30 were general patients presenting Eye OPD. Data of 30 patients were taken having keratoconus and 30 controls were compared with them with corneal scarring/opacity as a risk factor. Table 1 shows the corneal opacity is a significant risk factor of keratoconus, the p value is 0.042. Data of 30 patients were taken having keratoconus and 30 controls were compared with them with history of eye allergy as risk factor.

Table 1: Participant groups.

		Groups		Total	p value
		Case	Control		
Corneal opacity	yes	9	2	11	0.042
	No	21	28	49	
Total		30	30	60	

Table 2 shows the ocular allergy has a significant figure which is 0.004. Data of 30 patients were taken having keratoconus and 30 controls were compared with them with asthma as a risk factor. Data of 30 patients were taken having keratoconus and 30 controls were compared with them with Marfan syndrome as a risk factor.

Table 2: The ocular allergy.

		Groups		Total	p value
		Case	Control		
Asthma	Yes	7	0	7	0.011
	No	23	30	53	
Total		30	03	60	

Table 3: Down syndrome in group.

		Groups		Total	p value
		Case	Control		
Down Syndrome	Yes	2	0	2	0.492
	No	28	30	58	
Total		30	30	60	

Table 4: Mar fan Syndrome.

		Groups		Total	p value
		Case	Control		
Marfan Syndrome	Yes	1	0	1	1.00
	No	29	30	59	
Total		30	30	60	

DISCUSSION

In this case control research, it is found that the environmental risk factors for keratoconus are more prevalent in Pakistani population than the genetic factors. Among various risk factors assessed, only ocular allergy, corneal scarring/opacity and asthma are found to be the main risk factors for keratoconus in Pakistani population. Other systemic associations include retinitis pigmentosa, ectopia lentis and ulcerative colitis. Clinically many ocular and systemic disorders are associated with keratoconus but statistically many of them as cousin marriage and connective tissue diseases were noted to be insignificant in Pakistani population. Allergies have been found to be the most prevalent causative factor in keratoconus patients than controls in all worldwide studies.^{1,2,3,5,8,9,11,12,13,14,15,16,17,18,19,20,21,22,23,24} Asthma is also reported as a potent factor for the cause of keratoconus. Furthermore, it is related to systemic allergies as well as breathing problems during sleep including obstructive sleep apnea. This study agrees with previous research conducted with asthma.

CONCLUSION

This case control study verified that out of 5 causal factors assessed only 3 were found significant in our population. The main environmental factor was ocular allergy which proved to be the most potent factor as it is featured with vigorous rubbing of eye leading to corneal thinning as well as other malformations of cornea. Corneal scarring is also related to eye rubbing followed by inflammations of the cornea as vernal kerato conjunctivitis. Another determined cause was asthma associated with breathing problems and consequently sleeping disorders.

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REFERENCES

- Ozkurt Y, Atakan M, Gencaga T, Akkaya S. Contact lens visual rehabilitation in keratoconus and corneal keratoplasty. *J Ophthalmol* 2012;1:832070.
- Karsenas AG, Ruben M. Aetiology of keratoconus. *Brit J Ophthalmol* 1976;60:522-5.
- Kok YO, Tan GF, Loon SC. keratoconus in Asia. *Cornea* 2012;31:581-93.
- Bechrakis N, Blom ML, Stark WJ, Green WR. Recurrent keratoconus. *Cornea* 1994;13:73-7.
- Gokhale NS. Epidemiology of keratoconus. *Ind j Ophthalmol* 2013;61:382-3.
- Krachmer JH, Feder RS, Belin MW. Keratoconus and related noninflammatory corneal thinning disorders. *Sur Ophthalmol* 1984;28:293-322.
- Rabinowitz YS. Keratoconus. *Sur Ophthalmol* 1998;42:297-319.
- McMonnies CW, Boneham GC. Keratoconus, allergy, itch, eye-rubbing and hand-dominance. *Clin Exp Optom* 2003;86:376-84.
- Davidson AE, Hayes S, Hardcastle AJ, Tuft SJ. The pathogenesis of keratoconus. *Eye* 2014;28:189-95.
- Pihlblad MS, Schaefer DP. Eyelid laxity, obesity, and obstructive sleep apnea in keratoconus. *Cornea* 2013;32:1232-6.
- Davidson AE, Staves S, Hardcastle AS, Tuft SJ. The pathogenesis of keratoconus. *Eye* 2014;28:189-95.
- Mc Monnies LW. Abnormal rubbing and keratectasia. *Eye Cont Lens* 2007;33:265-71.
- Bawazeer AM, Hodge WG, Lorimer B. Atopy, and keratoconus: a multivariate analysis. *Br J Ophthalmol* 2000;84:834-6.
- Weed KH, MacEwen CJ, Cox A, McGhee CN. Quantitative analysis of corneal microstructure in keratoconus utilising in vivo confocal microscopy. *Eye* 2007;21:614-23.
- The Dundee University Scottish Keratoconus study: demographics, corneal signs, associated diseases, and eye rubbing. *Eye* 2008;22:534-41.
- Mc Monnies CW. Mechanisms of rubbing related corneal trauma in keratoconus. *Cornea* 2009;28:607-15.
- Mascai MS, Varley GA, Krachmer JH. Development of keratoconus after contact lens wear. Patient characteristics. *Arch Ophthalmol* 1990;108:534-8.
- Yeniad B, Alparslan N, Akarcay K. Eye rubbing as an apparent cause of recurrent keratoconus. *Cornea* 2009;28:477-9.
- Sugar J, Mascai MS. What causes Keratoconus? *Cornea* 2012;31:716-9.
- Jafri B, Lichter H, Stulting RD. Asymmetric keratoconus attributed to eye rubbing. *Cornea* 2004;23:560-4.
- Jacq PL, Sale Y, Cochener B, Lozach P, Colin J. Keratoconus, changes in corneal topography and allergy. Study of 3 groups of patients. *J francais d'ophthal* 1997;20:97-102.
- Tabbara KF. Ocular complications of vernal keratoconjunctivitis. *Can J Ophthalmol* 1999;34:88-92.
- Khan MD, Kunai N, Saeed N, Gulab A, Nazeer AF. Incidence of keratoconus in spring catarrh. *Br J Ophthalmol* 1988;72:41-3.
- Khan SB, Saleem M, Khalid MK, Ahmad I, Khan MD. Keratoconus and its association with other ocular diseases. *Pak J Ophthalmol* 2007;23:212-7.

Frequency of complications in endoscopic sinus surgery: while using all preventive measures documented in literature

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Objective: To assess the rate of different complications of endoscopic sinus surgery and to identify the factors linked to these complications.

Methodology: This prospective descriptive cross-sectional study included 52 patients who underwent endoscopic sinus surgery between 2020 and 2022, without a control group. The study evaluated patient symptoms, recurrent cases, intraoperative and postoperative complications. To analyze the data, a univariate analysis was conducted using SPSS 22.

Results: Out of 52 patients, 30 (57.7%) were females and 22 (42.03%) males. The most prevalent diagnosis was ethmoidal polyps, accounting for 42.03% of the cases, followed by chronic rhinosinusitis at 38.5% and

allergic fungal rhinosinusitis at 11.5%. Recurrent cases made up 5.77% of the total. Fortunately, none of the patients experienced any major complications. Only 15.38% (8 out of 52) of the patients developed minor complications like post-operative adhesions and temporary anosmia.

Conclusion: When patients are properly prepared before surgery, endoscopic sinus surgery produces significantly better outcomes with minimal complications. Improvement in symptoms is expected in more than 90% of patients with a minimal risk of recurrence and complications.

Keywords: Chronic sinusitis, complications, endoscopic sinus surgery, CSF leak, hemorrhage.

INTRODUCTION

Functional endoscopic sinus surgery (FESS) is presently recognized as the most successful treatment for chronic sinusitis (CRS) that does not respond to medical therapy and about 90% of patients report improvement following this procedure.¹ It is recommended for various conditions such as nasal polyps, dacryocystitis, repair of base of skull defects, correction of blow out fractures, removal of tumors in the base of the skull, paranasal sinuses, nasopharynx, and pituitary glands.² FESS can address orbital complications associated with sinusitis, perform orbital decompression for thyroid orbitopathy, relieve optic nerve compression, and remove necrotic tissues in cases of mucormycosis.^{1,3}

FESS is an advanced surgical procedure that has significantly transformed the treatment of sinus diseases.^{4,5} However, as the paranasal sinuses are adjacent to the orbit and cranial cavity, this technique poses the risk for serious complications.^{2,6} The most frequently encountered complications include development of synechia, and closure of the antrostomy (surgical opening into the maxillary sinus).^{3,7,8}

Major complications associated with the procedure comprise of extra-ocular muscle injury, persistent diplopia, internal carotid artery injury, nasolacrimal duct injury, orbital hemorrhage, or hematoma (blood accumulation), optic nerve injury, blindness,

subperiosteal and intra orbital abscesses, orbital cellulitis, enophthalmos, cerebrospinal fluid (CSF) leakage leading to meningitis and cavernous sinus thrombosis. Minor complications include periorbital ecchymosis, orbital emphysema, transient diplopia, the formation of synechia and anosmia.^{3,9,10} These complications can be effectively managed through a three-phase approach: preoperative, intraoperative, and postoperative.¹¹ By implementing diligent precautions during each phase, the probability of complications can be significantly reduced.^{2,12}

Prior to undergoing ESS, it is crucial to provide patients with comprehensive preoperative counseling about the associated risks, benefits and expected outcomes of the proposed procedure.^{1,7} Preoperative endoscopy and a systematic evaluation of imaging can help to identify anatomical variants that may lead to complications.^{2,10} During the surgery, careful handling of instruments and conservation of the mucosal lining are crucial technical considerations that can decrease the possibility of complications.^{1,3} Attentive postoperative care is essential to promptly identify any arising complications and initiate appropriate treatment to prevent long-term complications.¹ The objective of this study was twofold: firstly, to assess the occurrence rate of different complications following both primary and revision FESS while incorporating the preventive measures outlined in existing literature, and secondly, to identify the factors

associated with these complications within our healthcare setting.

METHODOLOGY

This prospective, descriptive, cross-sectional study was performed at PAF Hospital, Islamabad from January 2018 to January 2023. This study comprised of a total of 52 patients who underwent FESS during this period. There was no control group included in the study.

All patients requiring FESS were included, while those who declined to participate, failed to comply with instructions, or missed follow-up visits were excluded from the study. Throughout the study, various preventive measures were implemented before, during, and after the surgical procedure: Thorough patient histories were recorded, focusing on previous surgical procedures, drug usage, autoimmune conditions, history of trauma, coagulopathies, use of anticoagulant medications, blood pressure control and the ongoing medical management of the disease. The parameters considered for evaluation included patient symptoms, recurrent cases, as well as intraoperative and postoperative complications.

The patients were evaluated through a comprehensive endoscopic examination to evaluate the specific conditions of the patients. A preoperative review of imaging studies was conducted to identify any anatomical variations that could potentially impact the surgery and increase the risk of complications. The preoperative radiographic findings, particularly from CT scans, were thoroughly examined to identify areas of increased risk. Specific areas of interest included the depth of the cribriform plate, the slope of the lateral lamella, the integrity of the lamina papyracea, the presence of Onodi cells (ethmoidal air cells located posterior to the sphenoid sinus), optic nerve dehiscence, sphenoid sinus pneumatization, the position of the internal carotid artery (ICA), integrity of the skull base, the position of the ethmoid artery and the status of the uncinate process.

Additionally, three-dimensional CT scans of the frontal sinuses of the patients were analyzed in detail before the surgery. As part of the preoperative preparation, patients were administered prednisolone at a dosage of 1mg/kg of body weight and clarithromycin at a dosage of 500mg twice daily. This regimen was initiated at least 15 days prior to the scheduled surgery.

During the intraoperative phase, thorough topical preparation with effective vasoconstriction was performed to optimize the surgical field. To prevent bleeding during the surgery, Merocel surgical patties soaked in a solution of 1:1000 adrenaline was applied topically. The anesthetist was also requested to

administer hypotensive anesthesia with bradycardia. The speed of the microdebrider was maintained between 3000-4000 rpm to ensure precise control.

After the surgery, patients were instructed to perform regular nasal douching using a combination of steroid and saline solution to prevent crusting, adhesions and recurrence. Patients received proper medical treatment which included the administration of antibiotics to manage any postoperative infections. A comprehensive follow-up record was maintained for a period of two years.

Statistical Analysis: Data were analyzed by SPSS version 22. A univariate analysis and one sample t-test were used. $p < 0.05$ was considered significant.

RESULTS

A total of 52 patients were included in the study, with a mean age of 46.8 years. Among them, the majority were female, 32 (61.5%); the number of male patients was 20 (38.46%). Out of the 52 patients, 16 (30.8%) presented with polyps, 10 (19.2%) had CRS, 8 (15.4%) were diagnosed with allergic fungal rhinosinusitis (AFRS), 14 (26.9%) had dacryocystitis, 4 (7.7%) experienced cerebrospinal fluid rhinorrhea (CSF), and 4 (7.7%) were diagnosed with mucormycosis (Table 1).

Among the patients included in the study, FESS was performed in 34 patients (65.38%). These patients had a diagnosis of nasal polyps, CRS, or AFRS. Endoscopic dacryocystorhinostomy (Endo DCR) was performed in

Table 1: Proportion of participants with respect to their diagnosis and surgical procedure applied and post-op complications.

Diagnosis and procedures	Frequency N=52	%
Diagnosis		
Ethmoidal polyp	16	30.8
Dacryocystitis	14	26.9
CRS	10	19.2
AFRS	8	15.4
CSF Leakage	4	7.7
Surgical procedure		
FESS	32	61.5
ENDO-DCR	12	23.1
END. Debridement	4	7.7
CSF Leakage repair	4	7.7

10 patients (19.23%), while endoscopic repair of CSF leak was performed in 4 patients (7.7%). Additionally, 4 patients (7.7%) underwent endoscopic debridement (Table 1).

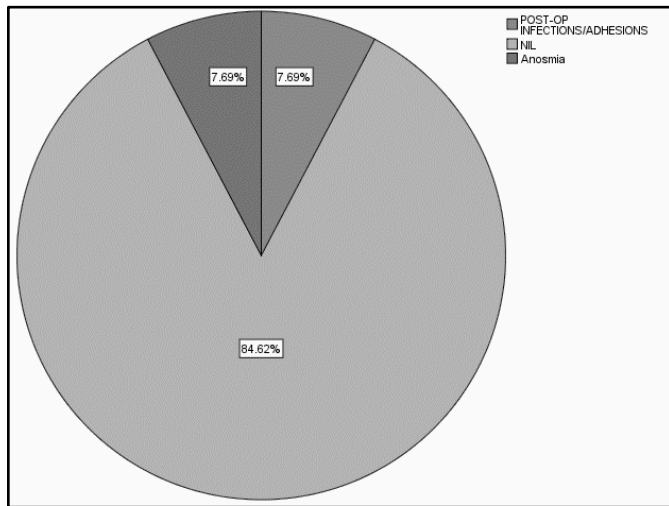


Fig. 1: No of postoperative complications (anosmia=7.69%, infection and adhesions=7.69%, no complications=84.6%).

During the follow-up examination, it was found that only 8 (15.38%) patients developed minor complications. Out of these, 4 patients (7.69%) experienced anosmia while 4 patients (7.69%) developed postoperative adhesions and infection. However, the majority of patients, 44 in total (84.6%), did not experience any complications following the surgery (Fig. 1). Importantly, none of the patients included in the study developed any major complications. The number of participants developed complications are significantly lower as p-value is <0.001 (95% CI=6.75, 7.10) on applying one-sample t-test.

DISCUSSION

Proper management of the patients after the procedure plays a crucial role in achieving optimal outcomes following FESS, alongside intricate and careful surgical techniques.^{2,13} Complications that may arise following FESS can be categorized into three groups. Immediate postoperative complications include bleeding and crusting, which are commonly observed during the initial stages of recovery. Short-term complications encompass issues such as infection, formation of synechiae, and lateralization of the turbinates. Long-term complications involve conditions like ostial stenosis, refractory disease, and disease recurrence.^{2,3,14}

These complications can further be classified as major or minor, based on their severity and impact on the patient's well-being. By understanding and addressing these

different types of complications, healthcare professionals can optimize patient care and minimize potential risks associated with FESS.

The available literature indicates that there is a learning curve associated with FESS. However, it is important to note that even highly skilled surgeons may still encounter complications during the procedure. Over time, as surgeons become more familiar and proficient with FESS, the incidence of complications has shown a significant decrease.

In our study, the findings are consistent with previous research that spans 25 years of experience. A considerable drop in FESS-related complications has occurred from 29%, with a frequency of 8% for major complications and 21% for minor complications, to approximately 3% to 5% currently.^{3,14} Our study is in line with the findings of the previously mentioned study and other previous studies in terms of the incidence of complications.

In our study, the overall rate of FESS-related complications was 15.8%, but it is important to note that all these complications were classified as minor. Among these minor complications, the most common were anosmia, synechiae and infections, each accounting for 7.69% of the cases.

In a previous study, it was reported that the incidence of major perioperative complications was 0.85%. Among these major complications, CSF leak was found to be the most common. On the other hand, minor complications were observed at a rate of 6.9% in that study.^{15,16}

The most frequently encountered minor complications were associated with orbital penetration and the formation of adhesions involving the middle turbinate.^{1,17,18} These findings highlight the importance of careful surgical technique and close monitoring to minimize the occurrence of both major and minor complications in ESS procedures.^{3,19}

CONCLUSION

Complications arising from FESS have the potential to cause substantial morbidity and even mortality. Even a slight deviation from surgical landmarks can lead to severe consequences such as intra-orbital and intracranial complications. Therefore, it is crucial to prioritize prevention over treatment. Preoperative preparation plays a vital role in mitigating complications. Thorough assessment of radiographic findings allows for identification of potential risk areas, aiding in appropriate decision-making. Strategic perioperative measures are also essential in minimizing the occurrence of complications.

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REFERENCES

1. Bruce K Tan, Rakesh K Chandra. Postoperative prevention and treatment of complications after sinus surgery. *Otolaryngol Clin North Am* 2010;43:769-79.
2. Al-Mujaini A, Wali U, Alkhabori M. Functional endoscopic sinus surgery: indications and complications in the ophthalmic field. *Oman Med J* 2009;24:70-4.
3. Stankiewicz JA. Complications of endoscopic sinus surgery. *Otolaryngol Clin North Am* 1989;22(4):749-58.
4. Hu KH, Lin KN, Li WT, Huang HM. Effects of Mero pack in the middle meatus after functional endoscopic sinus surgery in children with chronic sinusitis. *Int J Pediatr Otorhinolaryngol* 2008;72:1535-40.
5. Jameson M, Gross CW, Kountakis SE. Flo Seal use in endoscopic sinus surgery: effect on postoperative bleeding and synechiae formation. *Am J Otolaryngol* 2006;27:86-90.
6. Tewfik MA, Ten pearls for safe endoscopic sinus surgery. *Otolaryngol Clin North Am* 2010;43:933-44.
7. Bednarski KA, Kuhn FA. Stents and drug-eluting stents. *Otolaryngol Clin North Am* 2009;42:857-66.
8. Valentine R, Wormald PJ, Sindwani R. Advances in absorbable biomaterials and nasal packing. *Otolaryngol Clin North Am* 2009;42:813-28.
9. Iyengar JA, Svider PF, Setzen M. Clinical pearls in endoscopic sinus surgery: key steps in preventing and dealing with complications. *Am J Otolaryngol* 2014;35:324-8.
10. Adnane C, Adouly T, Zouak A, Mahtar M. Quality of life outcomes after functional endoscopic sinus surgery for nasal polyposis. *Am J Otolaryngol* 2015;36:47-51.
11. Rudmik L, Smith TL. Evidence-based practice: postoperative care in endoscopic sinus surgery. *Otolaryngologic Clin North Am* 2012;45:1019-32.
12. Tewfik MA, Wormald PJ. Ten pearls for safe endoscopic sinus surgery. *Otolaryngol Clin North Am* 2010;43:933-44.
13. Patel AM, Esq TE, Vaughan W. Medicolegal issues in endoscopic sinus surgery. *Otolaryngol Clin North Am* 2010;43:905-14.
14. Humphreys IM, Hwang PH. Avoiding complications in endoscopic sinus surgery. *Otolaryngol Clin North Am* 2015;48:871-81.
15. May M, Levine HL, Mester SJ, Schaitkin B. Complications of endoscopic sinus surgery: analysis of 2108 patients—incidence and prevention. *Laryngoscope* 1994;104:1080-3.
16. Abdulmajeed Alharbi, Fahad Alhussain, Abduljabbar Alyamani, Majed Aljohani. Complications of endoscopic sinus surgery for chronic rhinosinusitis in a tertiary care teaching hospital in Saudi Arabia. *Saudi Med J* 2023;44:601-6.
17. Homsy MT, Gaffey MM. Sinus Endoscopic Surgery. National Library of Medicine (NIH). Last Update: September 12, 2022.
18. Tunkel DE, Anne S, Payne SC, Ishman SL, Rosenfeld RM. Clinical Practice Guideline: Nosebleed (Epistaxis). *Otolaryngol Head Neck Surg* 2020;162:1-38.
19. Eloy P, Andrews P, Poirrier AL. Postoperative care in endoscopic sinus surgery: a critical review. *Curr Opin Otolaryngol Head Neck Surg* 2017;25:35-42.

Frequency of non-carious cervical lesions in patients requiring prosthodontic treatment at a teaching hospital in KPK, Pakistan: A cross-sectional study

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Objective: To determine the frequency of non-carious cervical lesions (NCCLs) relative to age among population requiring prosthodontic treatment at a teaching hospital in KPK.

Methodology: This cross-sectional study involving 213 participants aged 18 to 60 years was conducted. Participants relevant history was recorded followed by complete intraoral and extraoral examination to identify non-carious lesions. NCCL was stratified among age and gender to see effect modification, by using Chi square test.

Results: Tout of 213 patients, there were 134 males (62.9%) and 79 females (37.1%). The prevalence of NCCL was 71.8% (95% confidence interval). Among

18 to 40-year-old participants, the mean of NCCL was higher in males. Participants aged 41 to 60 years were more likely to present higher mean of NCCL. Out of 153 cases, the highest pattern was erosion 69 (45.1%) followed by abrasion 58 (37.9%) and abfraction 26 (17%).

Conclusion: The prevalence of NCCL was 71.8%, and it increased with advancing age. It is very important to recognize tooth wear in early stage, because treatment in case of pathological tooth wear usually requires extensive restorations.

Keywords: Tooth wear, prevalence, abrasion, dental, erosion.

INTRODUCTION

The tooth surface loss is common phenomenon observed in dental hard tissues. Caries is the primary cause for the loss of tooth structure that is directly linked to the pathological effect of different bacterial organisms. The tooth surface loss can also occur in the absence of caries in which the mechanical, chemical or both factors are involved.¹⁻⁴ The chemical effect is termed as erosion and mechanical effect is caused by abrasion and abfraction.⁵⁻¹⁰ The junction between cementum and enamel occurs at the cervical region of the tooth and has decreased enamel thickness.^{11,12} The mechanical abrasive effect of aggressive tooth brushing and the exposure of cementum with increasing age due to gingival recessions and periodontal problems are some of the common etiological factors.¹³ The etiology of such lesions is complex and cannot be specified.^{14,15}

Risk factors associated with the NCCLs are occlusion, age, gender, saliva, diet and para functional habits. Some display shallow grooves, and other includes broad, dished-out lesions or large, wedge-shaped defects with sharp line angles.^{16,17} NCCLs are most commonly found on facial surfaces and varies in appearance.¹⁸ Slight lesions cannot cause discomfort but severe lesions can cause hypersensitivity, painful sensation, pulp exposure and ultimately the death of the tooth.¹⁹

In a study found NCCL in 72.5% of subjects without gender discrimination and percentage of patients with

NCCL was higher in those people aging more than 40 years.²⁰ These lesions are commonly encountered in routine dental care and present a great challenge to the restoring dentist. The aim of this study was to provide data regarding the prevalence of non-carious cervical lesion in the population of KPK.

METHODOLOGY

This descriptive cross-sectional study was carried out at Bacha Khan Medical and Dental College, Mardan, KPK. Approval from hospital ethical committee was taken (Ethical number 630). An informed consent was taken from all participants.

Patients with age range of 18 to 60 years old, visiting the prosthodontics department with the grooves or notches that are not carious and present on the cervical area of the tooth on buccal and lingual surfaces were included in the study. The relevant history was recorded followed by complete intraoral and extraoral examination. The Sample size was 213 with non-probability consecutive technique and 95% confidence interval, 6% margin of error and keeping 72.5% proportion of non-carious cervical lesions.

Statistical Analysis: Data were analyzed using SPSS version 19. Chi square test was used. $p < 0.05$ was considered significant.

RESULTS

Among 213 cases, mean age of the patients was 38.5 ± 10.5 years. There were 134 males (62.9%) and 79 females (37.1%) (Table 1). Frequency of NCCLs amounted to 153 (71.8%). Out of these 153 cases, the highest pattern was erosion 69 (45.1%) followed by abrasion 58 (37.9%) and abfraction 26 (17%) (Table 2).

Table 1: Distribution of patients by age and gender.

Age (Year)	Number	%
18-40	124	58.2
41-60	89	41.8
Total	213	100.0
Mean$\pm$SD	38.5 ± 10.5	
Gender	Number	%
Male	134	62.9
Female	79	37.1

Table 2: Distribution of patients by non-carious cervical lesions (NCCLs) and its Type.

NCCLs	Number	%
Yes	153	71.8
No	60	28.2
Total	213	100.0
Types of NCCLs	Number	%
Erosion	69	45.1
Abrasion	58	37.9
Abfraction	26	17.0
Total	153	100.0

NCCL was stratified among age and gender to see effect modification, by using chi square test (Table 3).

DISCUSSION

The NCCLs are mostly misunderstood as compared to lesions caused by caries. It has been discussed quite frequently in literature, but it is still a controversial topic because of its multiple and complex etiology. It has been investigated in various populations over the world and multiple contradictory results have been observed. The incidence of NCCLs without caries has a prevalence rate of 5 to 85% among various regional populations. Brazilians between 40 and 60 years old reported NCCLs prevalence of 67% while in Chinese population from 35

to 74 years old presented a prevalence of 81.3%.⁶ In our study, the frequency of NCCLs was 71.3% in age group between 18 to 60 years old and the lesion was dominant among male individuals.

Table 3: Stratification for age and gender.

Age	Non-carious Cervical Lesions		Total	P value
	Yes	No		
18-40	78	46	124	0.001
41-60	75	14	89	
Total	153	60	213	
Gender				
Male	110	24	134	<0.001
Female	43	36	79	
Total	153	60	213	

Among different risk factors the most commonly observed are older age, chemical and mechanical factors that are strongly related to such lesion as mentioned in the bergstorm and lavsted study.^{21,22} The factors that are most commonly associated with NCCLs are erosion abrasion and abfraction. In our study, the most common factor observed was erosion 69%, which can be due to acidic diet, GERDs, asthma and medications.^{23,24} The limitations of the study are that the number and location of the lesions could be further investigated in comparatively greater sample size and older age groups.

CONCLUSION

The study concludes that non-carious cervical lesions are mostly observed in males and related to older age groups. The most common etiologic factor was erosion followed by abrasion and abfraction.

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REFERENCES

1. Yan W, Yang D. The prevalence, characteristics and risk factors in non-carious cervical lesion: A survey on 295 people in Guangzhou area. J Oral Hyg Health 2014;2:1-4.
2. Castaneda RZ, Magdaleno MO, Trancoso RCU. Restorative Rehabilitation of a Patient with Generalized Non-Carious Cervical Lesions: Case Report 2019;21:1-20.
3. Zafar Q, Qureshi B, Sattar S, Khalid H. Frequency of

- possible factors associated with Non-Carious Cervical lesions in permanent teeth. *Pak Oral Dent J* 2020;40:88-91.
4. Gomes RR, Zeola LF, Barbosa TAQ, Neto AFJ3, Almeida GA, Soares PV. Prevalence of non-carious cervical lesions and orthodontic treatment: a retrospective study. *Prog Orthod* 2022;23:1-7.
5. Ahmed H, Sadaf D, Rahman M. Factors associated with Non-Carious Cervical Lesions (NCCLs) in teeth. *J Coll Phys Surg Pak* 2009;19:279-82.
6. Lai ZY, Zhi QH, Zhou Y, Lin HC. Prevalence of non-carious cervical lesions and associated risk indicators in middle-aged and elderly populations in Southern China. *Chin J Dent Res* 2015;18:41-50.
7. Luhers AK, Guhr SJ, Gunau H, Herrmann P. Composite restorations placed in non-carious cervical lesions—Which cavity preparation is clinically reliable?. *Clin Exp Dent Res* 2020;6:558–67.
8. Brandini DA, Sousa ALB, Trevisan CI, Pinelli LA, Couto Santos SC, Pedrini D, et al. Noncarious cervical lesions and their association with toothbrushing practices: in vivo evaluation. *Oper Dent* 2011;36:581-9.
9. Haralur SB, Alqahtani AS, AlMazni AS, Alqahtani MK. Association of Non-Carious Cervical Lesions with Oral Hygiene Habits and Dynamic Occlusal Parameters. *Diagnostics* 2019;9:43:1-8.
10. Kolak V, Pešić D, Melih I, Lalović M, Nikitović A, Jakovljević A. Epidemiological investigation of non-carious cervical lesions and possible etiological factors. *J Clin Exp Dent* 2018;10:e648-e56.
11. Que K, Guo B, Jia Z, Chen Z, Yang J, Gao P. A cross-sectional study: non-carious cervical lesions, cervical dentine hypersensitivity and related risk factors. *J Oral Rehabil* 2013;40:24-32.
12. Alam M, Shah HM, Alam L, Shah A J P, Bibi A. The Relation between Non-Carious Cervical Lesions and Possible Etiological Factors – A Study from a Tertiary Care Setting of Pakistan. *Pak Armed Forces Med J* 2022;72:136-9.
13. Yoshizaki KT, Rios LFFD, Sobral MAP, Aranha ACC, Mendes FM, Scaramucci T. Clinical features and factors associated with non-carious cervical lesions and dentin hypersensitivity. *J Oral Rehabil* 2017;44:112-18.
14. Jakupovic S, Vukovic A, Korac S, Tahmiscija I, Bajsman A. The prevalence, distribution and expression of noncarious cervical lesions (NCCL) in permanent dentition. *Mater Sociomed* 2010;22:200-4.
15. Jafari Z. The study of possible factors related to Non-Carious Cervical Lesions. *Eur J Acad Essays* 2014;1:45-8.
16. Kumar S, Acharya S, Mishra P, Debnath N, Vasthare R. Prevalence and risk factors for dental erosion among 11- to 14-year-old school children in South India. *J Oral Sci* 2013;55:329-36.
17. Medeiros TLM, Mutran SCAN, Espinosa DG, Faial KDCF, Pinheiro HHC, Couto RSDA. Prevalence and risk indicators of noncarious cervical lesions in male footballers. *BMC Oral Health* 2020;20:215:1-9.
18. Peumans M, Politano G, Meerbeek BV. Treatment of noncarious cervical lesions: why, when and how. *The Int J Esthet Dent* 2020;15:16-42.
19. Jiang H, Du MQ, Huang W, Peng B, Bian Z, Tai BJ. The prevalence of and risk factors for non-carious cervical lesions in adults in Hubei Province, China. *Commun Dent Health* 2011;28:22-8.
20. Khan S, Khan A, Rehman A, Sajid M, Saeed A, Khan AJ. Frequency and severity levels of non-carious cervical lesions in abutments to be used for fixed dental prosthesis. *Professional Med J* 2022;29:482-6.
21. Bergstorm J, Lavstedt S. An epidemiologic approach to toothbrushing and dental abrasion. *Community Dent Oral Epidemiol* 1979;7:57-64.
22. Daniela NR, Teixeira DN, Thomasa RZ, Soaresb PV, Cunea MS, Gresnigt MM et al. Prevalence of nonserious cervical lesions among adults: A systematic review. *J Dent* 2020;95:1-8.
23. Schlueter N, Luka B. Erosive tooth wear – a review of global prevalence and its prevalence in risk groups. *Br Dent J* 2018;224:364–70.
24. Warreth A, Abuhijleh E, Almaghribi MA, Mahwal G, Ashawish A. Tooth surface loss: a review of literature. *Saudi Dent J* 2020;32:53–60.

Prevalence of temporomandibular joint disorders and their association with anxiety and bruxism in dental students and house officers: a cross-sectional study from Punjab, Pakistan

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Objective: To identify prevalence of temporomandibular joint disorders (TMD) and their association with anxiety and bruxism in dental students and house officers in Punjab, Pakistan.

Methodology: This cross-sectional study was conducted in two private dental institutes of Punjab from February 2022 to March 2023, on BDS students and house officers diagnosed with at least one symptom of TMD after screening. We used Diagnostic Criteria for the Most Common Intra-Articular Temporomandibular Disorders self-administered questionnaire and Patient Health Questionnaire (PHQ-4).

Results: Out 433 participants, 141 (32.5%) had TMD pain; more than half were females, and around one-third were house officers (n=50, 35.5%). The mean PHQ score was 5.11 ± 2.46 , falling in the moderate anxiety range. Female patients (p=0.026), bruxers (p=0.023), those with myofascial pain (p=0.034), headaches

(p=0.001), and referred myofascial pain (p=0.025) had significantly higher mean PHQ scores. The top three findings were disc displacement with reduction (n=16, 47%), headache (n=12, 35.2%) and local myalgia (n=12, 35.2%). A significantly higher proportion of females with TMD reported local myalgia (p=0.045), and a significant proportion of respondents with TMD and bruxism reported local myalgia (p=0.002).

Conclusion: The anxiety levels, as well as myofascial pain, among the female respondents and bruxers suffering from TMDs were significantly higher. Myofascial discomfort, headaches, and disc displacement with reduction were the most common symptoms. The results highlight the significance of mental health education, routine evaluations, and therapies for dental students with TMDs.

Keywords: Bruxism, chronic pain, dental care, temporomandibular joint disorders.

INTRODUCTION

Temporomandibular joint disorders (TMDs) encompass a group of multifactorial conditions affecting the temporomandibular joint (TMJ) and the surrounding structures, leading to pain, dysfunction, and impairment of jaw movements.¹ TMDs are among the most prevalent orofacial pain disorders worldwide, with a significant impact on individuals' quality of life.² The etiology is complex and may involve biological, psychological, and social factors.^{1,3} Epidemiological studies from various regions have reported varying prevalence of TMDs, suggesting possible regional and cultural differences in susceptibility to the disorder.³ Studies have shown differing prevalence rates between Asian and Western populations.^{2,4} Cultural nuances, dietary habits, genetic factors, and even differences in the diagnosis and reporting can account for such variations.⁵

Anxiety is a common mental health condition characterized by excessive worry, fear, and

apprehension, often accompanied by physical symptoms such as muscle tension and restlessness.^{1,4} Dental anxiety, in particular, is prevalent among individuals seeking dental care, and it can significantly affect the oral health-seeking behavior of affected individuals.^{6,7} Given the anatomical proximity of TMJ to the dental structures and the role of stress in triggering or exacerbating TMD symptoms, it is essential to explore the potential relationship between TMDs and anxiety.³ Understanding the interplay between TMDs and anxiety is crucial as it may influence disease management and patient outcomes.⁷

Anxiety-related bruxism, a parafunctional habit of teeth grinding or clenching during sleep or wakefulness, is commonly associated with TMDs and may exacerbate the condition.⁸ Moreover, the presence of chronic pain and dysfunction resulting from TMDs can also contribute to increased anxiety levels in affected individuals.⁹ This study aimed to explore the prevalence of TMDs among

Table 1: PHQ scores in relation to gender, bruxism, and various TMD findings.

Groups		n (%)	Mean±SD	Median (IQR)	U	P-value
Gender	Male	50 (35.4)	4.44±2.06	4 (9)	2786	0.026*
	Female	91 (64.5)	5.48±2.59	5(4)		
Bruxism	Present	30 (21.2)	6.03±3.23	6(7)	1287	0.023*
	Absent	109 (77.3)	4.83±2.14	4(3)		
Disc displacement with reduction	Present	57 (40.4)	5.05±2.56	4(4)	2035.0	0.657
	Absent	84 (59.5)	5.15±2.40	5(4)		
Local myalgia	Present	43 (30.4)	5.26±2.62	5(4)	1889.5	0.745
	Absent	98 (69.5)	5.05±2.40	4(3)		
Myofascial pain	Present	61 (43.2)	5.67±2.61	5(5)	1936.0	0.034*
	Absent	80 (56.7)	4.69±2.26	4(3)		
Headache attributed to TMD	Present	57 (40.4)	6.89±2.38	7(4)	763.0	<0.001*
	Absent	84 (59.5)	3.90±1.66	4(2)		
Disc displacement with reduction with intermittent locking	Present	26 (18.4)	5.77±2.61	4.5(4)	1214.0	0.131
	Absent	115 (81.5)	4.97±2.41	4(4)		
Myofascial pain with referral	Present	31 (21.9)	6.06±2.72	6(5)	1261.0	0.025*
	Absent	110 (78.0)	4.85±2.33	4(3)		
Disc displacement without reduction with limited mouth opening	Present	21 (14.8)	5.33±2.12	5(4)	1132.5	0.455
	Absent	120 (85.1)	5.08±2.52	4(4)		

P-values were obtained using the Mann-Whitney U test.

dental students and house officers in Punjab while investigating the potential association of TMDs with bruxism and anxiety.

METHODOLOGY

This cross-sectional analytical study was conducted at the two private dental institutes from 1st February 2022 to 31st March 2023 after approval from IRB of the University College of Medicine and Dentistry (Ref No: UCD/ERCA/22/12j). A total of 433 volunteers participated in the study; the consecutive sampling technique was employed. The inclusion criteria were undergraduate students from 1st year BDS to final year BDS and house officers who agreed to participate in the study. Considering a 95% confidence interval, a 5% margin of error, and an estimated prevalence of 31% derived from a prior study.¹⁰ The initial calculation yielded a sample size of 327 participants. However, to enhance the representation of our sample and account for potential attrition, the sample size was subsequently

increased to 433 participants.

An already validated DC/TMD (Diagnostic Criteria for the Most Common Intra-Articular Temporomandibular Disorders) self-administered questionnaire was utilized.¹¹ Forms were distributed to clinical students and house officers during their clinical rotations. For students in non-clinical years, the distribution took place at the conclusion of lectures, after the consent of the respective lecturers. The forms were collected and then checked for completion. The responses were screened by a postgraduate trainee.

After written consent, respondents who reported TMD pain or had at least one positive TMD symptom were invited to the dental clinic for complete TMJ evaluation by an experienced faculty member from the Oral and Maxillofacial Dentistry Department. The same faculty member evaluated all participants to avoid bias. A standardized diagnostic approach involving history and clinical examination for various disorders was followed. After evaluation, the history of bruxism was documented,

and an ultra-brief tool, the Patient Health Questionnaire (PHQ-4), for detecting anxiety and depression was filled by the participants who were evaluated in the clinic. PHQ-4 is a four-item patient health questionnaire for anxiety and depression and has a scoring criterion of normal (0-2), mild (3-5), moderate (6-8), and severe (9-12) anxiety and depression.¹²

Statistical Analysis: The data were analyzed using SPSS version 24, (IBM Corporation, USA). The normality of the data was assessed with Shapiro-Wilk's test. The data were not normally distributed; therefore, a non-parametric test, i.e., the Mann-Whitney U test, was applied to compare the means. The Chi-Square Test was used to compare percentages of categorical variables. A p value less than or equal to 0.05 was taken as significant.

RESULTS

In the study, 433 participants underwent screening.

Among them, 264 (61%) were female and 169 (39%) males. Out of those who were screened, 141 individuals (32.5%) displayed either TMD pain or at least one positive TMD symptom. Among these, females constituted a majority of 64.5% (91 individuals), while males comprised 35.5% (50 individuals). The majority of respondents were either final-year BDS students (41.8%, 59 individuals) or house officers (36.1%, 51 individuals). Additionally, 14.3% (20 individuals) were from the third year of BDS, and 7.8% (11 individuals) were from the second year.

The mean PHQ score was 5.11 ± 2.46 , falling in the moderate anxiety range. Female patients ($p=0.026$) and patients with bruxism ($p=0.023$), myofascial pain ($p=0.034$), headaches attributed to TMJ ($p<0.001$), and referred myofascial pain ($p=0.025$) had significantly higher mean PHQ scores, indicating higher stress levels (Table 1).

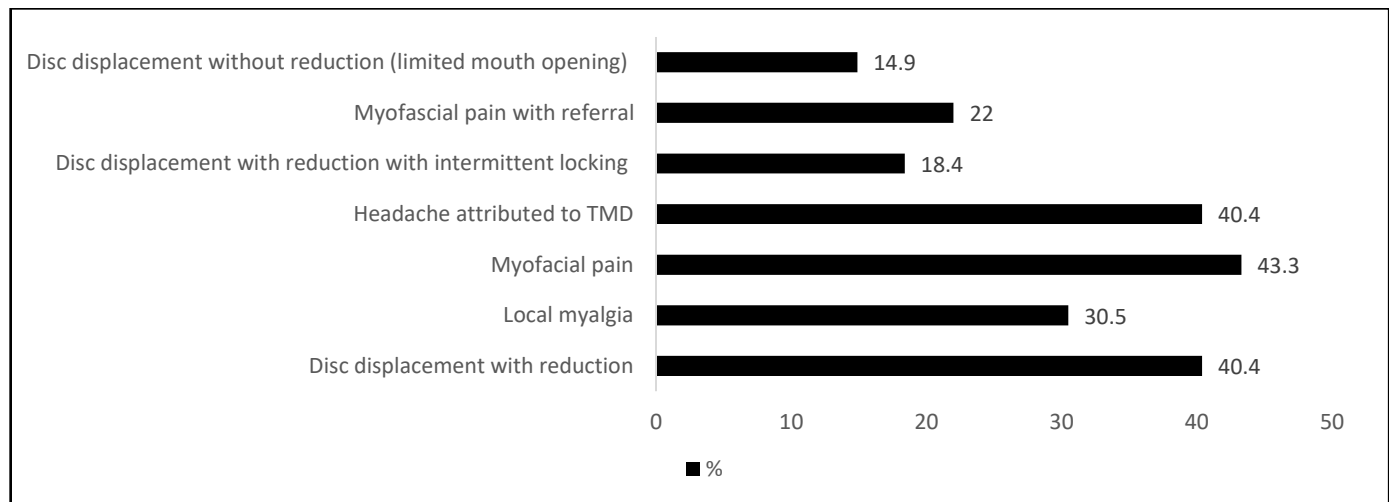


Fig. 1: Frequency of various TMD findings.

Table 2: Various TMD symptoms in relation to gender.

TMD's	Gender		X ²	p-value
	Male (%)	Female (%)		
Disc displacement with reduction	20 (40)	37 (40.6)	0.006	0.939
Local mialgia	10 (20)	33 (36.2)	4.02	0.045*
Myofascial pain	23 (46)	38 (41.7)	0.237	0.627
Headache attributed to TMD	17 (34)	40 (43.9)	1.32	0.249
Disc displacement with reduction with intermittent locking	8 (16)	18 (19.7)	0.307	0.580
Myofascial pain with referral	12 (24)	19 (20.8)	0.183	0.669
Disc displacement without reduction with limited mouth opening	7 (14)	14 (15.3)	0.049	0.825

P values were obtained using the Chi-square test

Table 3: Association of Bruxism with TMDs.

TMDs	Bruxism		X ²	p-value
	Present (%)	Absent (%)		
Disc displacement with reduction	12 (40)	45 (41.2)	0.147	0.701
Local mialgia	17 (56.6)	26(23.8)	10.00	0.002*
Myofascial pain	16 (53.3)	45(41.2)	0.766	0.382
Headache attributed to TMD	16 (53.3)	41(37.6)	1.57	0.209
Disc displacement with reduction with intermittent locking	8 (26.6)	18(16.5)	1.18	0.275
Myofascial pain with referral	7(23.3)	24(22.0)	0.001	0.986
Disc displacement without reduction with limited mouth opening	4(13.3)	17(11.9)	0.187	0.665

P values were obtained using the Chi-square test

The most frequent TMD findings have been illustrated in Figure 1. The association between the TMDs and gender is presented in Table 2. There was no statistically significant difference between the presentation of various TMDs between the male and female respondents, except in the case of local myalgia, where a significantly higher ($p=0.045$) proportion of females reported local myalgia. There was no statistically significant difference between the presence of bruxism among respondents presenting with various TMDs except in local myalgia. A significant ($p=0.002$) proportion of respondents suffering from bruxism had local myalgia (Table 3).

DISCUSSION

By examining a cross-section of this population, the study endeavors to quantify the prevalence of TMJ disorders and to discern any significant associations with psychological stress and habitual bruxism, both of which are common in the high-pressure environment of dental education and practice.^{1,2} A study from China by Wu et al reported that around 31.7% of medical university students had at least one TMD symptom, and the presence of psychological distress, including anxiety, depression, and sleep disturbances, was significantly more prevalent in them.¹³

A study from Saudi Arabia reported incidence of TMDs to be higher among female and clinical-level dental students.¹⁴ A correlation between myofascial pain and psychosocial distress was identified in a study done by Shabani et al.¹⁵ In the current study, around one-third of students had TMD pain and at least one positive TMD symptom, with a significant proportion from the clinical years. Higher stress scores were found in patients with myofascial pain and headaches associated with TMDs. These results were consistent with the findings of the

previous studies.

Individuals suffering from TMDs commonly experience pain as the most prevalent symptom, which can manifest in various areas, including the jaw, ear, temple, neck, or even the shoulders.¹⁶ A characteristic symptom reported is a clicking sound.¹⁷ Ear-related symptoms such as pain and tinnitus can also emerge. Some people describe facial pain that isn't localized to the jaw area.¹⁸ Additionally, due to the interconnected nature of the muscular system, pain can radiate to the neck and shoulder regions.¹⁴ In the present study, the top three symptoms were myofascial pain, headaches, and disc displacement with reduction, whereas the three least reported symptoms were myofascial pain, disc displacement without reduction, and intermittent locking.

Epidemiological studies consistently highlight a pronounced gender disparity in TMD, with females reporting its signs and symptoms more frequently than males.¹⁹ One of the significant factors believed to contribute to this discrepancy is the influence of female sex hormones, particularly estrogen. Fluctuations in these hormones during various life stages seem to correlate with exacerbated TMD symptoms in some women.²⁰ Moreover, differences in pain perception and reporting between genders might also play a role.

Cultural and societal norms may make women more proactive in seeking medical attention and voicing their symptoms.^{6,21} On the psychosocial front, there's speculation that women might internalize stress differently than men, which could influence TMD onset or severity.²² In the current study, the females with TMDs were more stressed. Moreover, local myalgia was more frequently reported in females. These findings were consistent with the previous studies.^{19,21,22,23}

Bruxism is frequently associated with TMD. This

grinding and clenching of teeth, often subconscious and predominantly during sleep, can exert excessive forces leading to wear and tear (of what), inflammation, and joint damage, manifesting as pain, reduced mobility, and clicking.²³ Bruxism can be a significant contributing factor to the development or exacerbation of TMD; however, not everyone with bruxism develops TMD.⁸ Medical students, given the rigorous demands and pressures of their academic environment, are particularly susceptible to high stress levels.¹ Several studies have shown a positive correlation between periods of heightened academic stress, such as exams or clinical rotations, and an increase in self-reported bruxism among medical students.^{1,3,23,24} In the current study, those suffering from bruxism had significantly higher anxiety and stress scores. Furthermore, those who were suffering from TMDs and had bruxism reported a higher frequency of myofascial pain.

The study's findings may have implications for healthcare providers, policymakers, and dental professionals in Pakistan and worldwide. Due to its cross-sectional nature, the study has captured data at a single point in time. There might be other confounding factors that could influence the prevalence of TMDs, such as physical trauma, genetic predisposition, and lifestyle factors.

CONCLUSION

TMDs were present in one-third of the individuals, with a higher incidence among females and house officers. There was a substantial association between TMDs and psychological distress, as evidenced by significantly higher mean PHQ scores in individuals with bruxism, myofascial pain, headaches, and referred myofascial pain. Notably, females with TMD exhibited higher stress levels. Individuals with bruxism exhibited significantly higher anxiety and stress scores, and those with both TMDs and bruxism reported a higher frequency of myofascial pain.

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REFERENCES

1. Ahuja V, Ranjan V, Passi D, Jaiswal R. Study of stress-induced temporomandibular disorders among dental students: An institutional study. *Natl J Maxillofac Surg* 2018;9:147–54.
2. Yakşi E, Demirel A, Yaşar MF, Kılınç S, Balcı M. The prevalence of temporomandibular disorders among medical students. *Northwestern Med J* 2023;3:38–44.
3. Osiewicz M, Lobbezoo F, Ciapała B, Pytko-Polończyk J, Manfredini D. Pain predictors in a population of Temporomandibular Disorders patients. *J Clin Med* 2020;9:452–6.
4. Nazir MA, Izhar F, Hassan S, Tanvir M, Nemat F, Ashraf MW, et al. Temporomandibular disorders among dental students in Pakistan: Assessment of prevalence, severity, and associated factors based on questionnaire. *Scientifica* 2023;2023:1–7.
5. Yap AU, Lei J, Fu KY, Kim SH, Lee B-M, Park JW. DC/TMD Axis I diagnostic subtypes in TMD patients from Confucian heritage cultures: a stratified reporting framework. *Clin Oral Investig* 2023;27:4459–70.
6. Chishti F, Hassan H, R. Qazi S. Dental anxiety among students of Lahore, Pakistan. *Pak J Med Health Sci* 2021;15:2659–61.
7. Reis PHF, Laxe LAC, Lacerda-Santos R, Münchow EA. Distribution of anxiety and depression among different subtypes of temporomandibular disorder: A systematic review and meta-analysis. *J Oral Rehabil* 2022;49:754–67.
8. Aditya A, Shailesh LE. Prevalence of symptoms associated with temporomandibular disorders in patients with psychosocial disorders. *J Int Dent Med Res* 2012;5:26–9.
9. Kleykamp BA, Ferguson MC, McNicol E, Bixho I, Arnold LM, Edwards RR, et al. The prevalence of comorbid chronic pain conditions among patients with temporomandibular disorders: A systematic review. *J Am Dent Assoc* 2022;153:241–50.
10. Valesan LF, Da-Cas CD, Réus JC, Denardin ACS, Garanhani RR, Bonotto D, et al. Prevalence of temporomandibular joint disorders: a systematic review and meta-analysis. *Clin Oral Investig* 2021;25:441–53.
11. van der Meer HA, Bakke M, Schytz HW, Madsen BK. Validation of the temporomandibular disorder pain screener in a specialized headache center. *J Oral Facial Pain Headache* 2021;35:150–6.
12. Ghaheer A, Omani-Samani R, Sepidarkish M, Hosseini M, Maroufizadeh S. The four-item Patient Health Questionnaire for anxiety and depression: A validation study in infertile patients. *Int J Fertil Steril* 2020;14:234–9.
13. Wu J, Huang Z, Chen Y, Chen Y, Pan Z, Gu Y. Temporomandibular disorders among medical students in China: prevalence, biological and psychological risk factors. *BMC Oral Health* 2021;21:1–8.
14. AlHussaini AA, AlHudithy LH, AlHadlaq MA, AlAzzam NF, Abahussain NW, AlDukhiel SA, et al. The prevalence and severity of temporomandibular disorder (TMD) among female dental students in Riyadh, Saudi Arabia.

- Saudi Dent J 2019;31:55–6.
15. Shabani M, Nazeri M, Ghahrechahi H-R, Pourzare A, Abareghi F, Samiee-Rad S, et al. Role of anxiety and depression in association with migraine and myofascial pain temporomandibular disorder. *Indian J Dent Res* 2018;29:583-7.
 16. Kapos FP, Look JO, Zhang L, Hodges JS, Schiffman EL. Predictors of long-term TMD pain intensity: An 8-year cohort study. *J. Oral Facial Pain Headache* 2018;32:113-22.
 17. Poluha RL, De la Torre Canales G, Bonjardim LR, Conti PCR. Clinical variables associated with the presence of articular pain in patients with temporomandibular joint clicking. *Clin Oral Investig* 2021;25:3633–40.
 18. Alkudhairy M, Al Ramel F, Al Jader G, Al Saegh L, Al Hadad A, Alalwan T, et al. A self-reported association between temporomandibular joint disorders, headaches, and stress. *J Int Soc Prev Community Dent* 2018;8:371-80.
 19. Bayat M, Abbasi AJ, Noorbala AA, Mohebbi SZ, Moharrami M, Yekaninejad MS. Oral health-related quality of life in patients with temporomandibular disorders: A case-control study considering psychological aspects. *Int J Dent Hyg* 2018;16:165–70.
 20. Stinson C, Bellinger LL, Puri J, Ahuja N, Bender SD, Kramer PR. Estrogenic effects on temporomandibular disorder and pain. *J Appl Biobehav Res* 2019;24:e12164.
 21. Samulowitz A, Gremyr I, Eriksson E, Hensing G. “brave men” and “emotional women”: A theory-guided literature review on gender bias in health care and gendered norms towards patients with chronic pain. *Pain Res Manag* 2018;2018:1–14.
 22. Bueno CH, Pereira DD, Pattussi MP, Grossi PK, Grossi ML. Gender differences in temporomandibular disorders in adult populational studies: A systematic review and meta-analysis. *J Oral Rehabil* 2018;45:720–9.
 23. Wieckiewicz M, Smardz J, Martynowicz H, Wojakowska A, Mazur G, Winocur E. Distribution of temporomandibular disorders among sleep bruxers and non-bruxers-A polysomnographic study. *J Oral Rehabil* 2020;47:820–6.
 24. van Selms MKA, Thymi M, Lobbezoo F. Psychological distress, and the belief that oral behaviors put a strain on the masticatory system in relation to the self-report of awake bruxism: Four scenarios. *J Oral Rehabil* 2023;42:63-8.

Patients' mental health data and Internet of Medical Things Safety: Analyzing Raspberry pi vulnerabilities

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Objective: To evaluate the safety of patient's data in an Internet of Medical Things (IoMT) ecosystem. The study focuses on these main objectives: To assess the vulnerability of IoMT devices and systems to cyber threats and data breaches. Specifically, we look at the vulnerability of the raspberry pi servers that are considered the essential building block of an IOT/IoMT environment; to pinpoint vulnerability areas of IoMT ecosystem; and to identify and propose mitigation strategies for the key risks associated with the IoMT ecosystem.

Methodology: The study employed setting up a representative IOMT model where a raspberry pi server controls the IOMT devices. An empirical analysis of a range of IoMT devices and systems was performed to identify specific vulnerabilities. This involved penetration testing and security assessments in controlled environments. We identified the mitigation strategies to gauge the effectiveness and tested the

effectiveness of the mitigation strategies.

Results: There were several critical vulnerabilities within the IoMT ecosystem such as weak encryption methods, lack of proper monitoring, effective authentication mechanisms, and the use of outdated software. The underlying raspberry pi server were vulnerable to common cyberattack vectors. However, such vulnerabilities could be countered by effective mitigation techniques allowing to capitalize on the IoMT ecosystem.

Conclusion: The study confirms the need for ongoing monitoring and improvement in the IoMT ecosystem. The healthcare practitioners and administrators need to put a string governance process in place to ensure the continuous monitoring of potential vulnerabilities and in turn providing an effective remedy.

Keywords: Critical cases, effective mitigation techniques, Internet of Medical Things, mental health, patient data.

INTRODUCTION

The Internet of Medical Things (IoMT) has emerged as a transformative force in healthcare, integrating digital and physical worlds to enhance medical care and patient outcomes. IoMT utilizes a network of plethora of connected devices, sensors, and software applications in order to facilitate real-time monitoring, data collection, and analysis. This rapid proliferation of IoMT has introduced significant security vulnerabilities and challenges that compromise the confidentiality, integrity, and availability of sensitive health data.^{1,2} The scenario is complicated further due to the extensive use of Big Data and Machine Learning practices, that can involve significant sensitive patient data.³⁻⁵⁷

Despite the enormous economic benefits of IoMT,⁶ the conflation of healthcare and information technology introduces unheralded security challenges.² The sensitivity and critical nature of health-related data^{1,7} and the ensuing legislation/compliance requirements necessitate a higher standard of protection, making the stakes for securing IoMT infrastructure exceptionally high.

This paper aims to provide a comprehensive analysis of IoMT vulnerabilities, the challenges they pose to securing the IoMT ecosystem and appropriate mitigation strategies for patients' data. Furthermore, we will discuss the regulatory steps and challenges that practitioners face in this realm.

METHODOLOGY

As specified,⁸ the approach to test the raspberry Pi security and in turn the IoMT attacks focused on the following vulnerabilities: Network access, Misconfiguration of devices, Operating System Attacks, Application Specific Attacks, Password Hacking and Man in The Middle Attack. The experimental setup is shown in the Fig. 1.

Specifically, we placed the Raspberry Pi server on the DMZ (Open to the public on the Internet), we installed the Apache and Nginx web server (allows anyone to connect to the server), we configured the SSH server that will allow other hosts to connect to it remotely, we installed the php server and made a sample application

that would allow upload of files and we used Kali server to run various threads of attacks with different attack vectors.

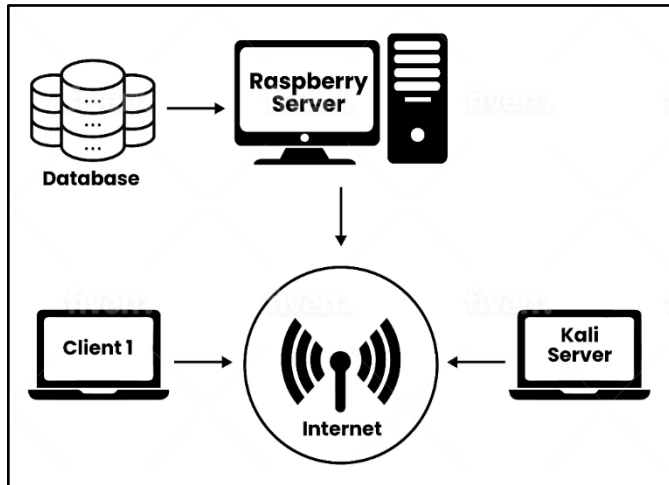


Fig. 1: The architecture of our experimental setup.

Test Cases were as follows:

1. `/tmp` default`: In this scenario, we used scripts to copy executable scripts into the `/tmp` directory. This type of attack is a typical backdoor that hackers look for and is known to be a common vulnerability.^{8,9} The default on many Linux/Raspberrys Pi distribution leaves this backdoor open to exploitation.
2. Privilege escalation using the sudo user list: In this scenario, the hacker would gain access to the account of any user on the system and try to gain access as administrator by exploiting the sudo feature vulnerability^{10,11} to access sensitive information.
3. Brute Force password hacking: The hacker would gain access by grabbing the list of users from the

`/etc/passwd` file and perform a dictionary attack to find passwords that are not complex.

4. Uploading a script using the file attachment feature: This test case involved uploading a malicious script using the file attachment feature. This scenario has been discussed in detail.¹²
5. Using Metasploit to exploit Apache vulnerability: Metasploit is a powerful tool used for security testing, specifically designed to aid in the discovery of vulnerabilities and the development of defense strategies against cyber threats.¹³ We focused on the Apache web server as listed in Sabetta et al.¹⁴
6. Brute Force ssh password attack: This scenario involved exploiting the secure shell (ssh) vulnerability that allows remote connection. This test case, combined with test case 3 described above, circumvents the password in a brute force/dictionary attack.
7. CSS and CSRF attack: This scenario deals with inherent vulnerabilities of Javascript where malicious code is injected in the user browser.
8. ARP spoofing/Man in the middle: In ARP spoofing/poisoning, the hacker sends fake Address Resolution Protocol (ARP) messages over a local area network (LAN) to fool the network into thinking that the hacker machine is the intended device on the network.

RESULTS

Table summarizes the results of different types of cybersecurity attacks tested against a sample of 1000 attack vectors, detailing the attack type, the specific vectors used, and the outcomes:

Table 1: Results of different types of cybersecurity attacks tested against a sample of 1000 attack vectors

Type of Attack	Attack Vector	Result
Test Case 1	Tmp vulnerability	Successful
Test Case 2	Brute Force dictionary attack to guess the password	Successful
Test Case 3	Brute Force password hacking	Successful
Test Case 4	Uploading malicious script	Successful
Test Case 5	Metasploit and Apache server vulnerability	Successful
Test Case 6	Brute Force ssh users	Successful
Test Case 7	CSS and XRSF vulnerability	Successful
Test Case 8	ARP spoofing	Unsuccessful

DISCUSSION

The first case exploits the `/tmp` directory exploit in Linux. The `/tmp` vulnerability in Linux refers to security weaknesses associated with the /tmp` directory, which is used as a temporary storage by both the system and applications running on a Linux-based system. This directory by default allows any authorized user on the system to write/delete files allowing hackers to exploit this`

vulnerability. The results confirmed the findings in Lincke.¹⁵ Practitioners can use the following mitigation practices as discussed in Alrawais et al:¹⁶

1. Making /tmp directory private: Latest updates to Linux allows the administrators to make this directory private and offer workarounds that are secure by design.
2. Access Controls: Administrators should ensure that default permissions are overridden and that the temporary files ownership should be set appropriately.
3. Effective Use of Sticky Bit: While the original Linux distributions allowed all users the ability to write/delete to the /tmp directory, the sticky bit (known as 't' permission) limits users from deleting or renaming files owned by other users.
4. Regular Monitoring and Cleanup: Automated tools allow administrators to effectively monitor and cleanup the contents of '/tmp' hampering the hackers' capability.

The second case exploits the sudo vulnerability. Specifically, hackers tend to exploit the security flaws discovered over time in the sudo utility to gain limited admin capability.^{15,17} Mitigation strategies for sudo vulnerabilities typically include the following:¹⁸

1. Installing Updated Software Patches: The patches are released regularly for such vulnerabilities.
2. Restricting Access of sudo Use: Limit the users that have sudo access.
3. Monitoring: Automated tools allow administrators to monitor such actions.

The third test case involved brute force techniques to guess the password for authorized users on the system.¹⁵ This type of attack is based on the premise that, given enough attempts, any password can eventually be guessed correctly. Simple and common passwords can often be cracked in a very short time, while more complex passwords take significantly longer.

As a mitigation strategy, administrators should do the following:

- 1) Put in a lockout policy where an account is locked after a certain number of failed login attempts.
- 2) Administrators should strictly enforce strong password policy which forces the users to choose "strong passwords" – a combination of special characters, numbers etc.¹⁸

The fourth test case – "attach file vulnerability" - usually occurs when an application does not properly validate or sanitize file inputs. Some mitigation strategies include the following:

1. Validation and Sanitization: Administrators should employ industry tools that validates such files and detect/prevent malicious scripts.

2. Size Limits: Administrators should also enforce size limits on file uploads.
3. Storage and Execution: Administrators should store uploaded files outside of the web root account for isolation purposes.
4. Appropriate Permissions: Administrators should set minimal permissions on uploaded files to prevent execution.
5. Anti-malware Scanning: Administrators should use automated tools to scan uploaded files for safety purposes.
6. User Authentication and Authorization: Administrators should restrict file upload capabilities to authenticated users only with absolute minimal permissions.

The fifth case deals with the web server vulnerabilities. Hackers exploit such flaws to gain unauthorized access, steal data, perform denial-of-service attacks, or execute malicious code.¹⁹ Mitigation strategies include the following:

1. Regularly Update and Patch: Administrators should keep the web server and all related software up to date with the latest security patches.
2. Secure Configuration: Administrators should follow best practices for server configuration, disable unnecessary services, and use secure settings.
3. Security Scanners and Tools: Administrators should utilize tools to scan for vulnerabilities, misconfigurations, and known weaknesses.
4. Firewalls and Intrusion Detection Systems (IDS): Administrators should deploy firewalls and IDS to monitor and filter malicious traffic.
5. Minimize Server Information Disclosure: Administrators should configure the server to disclose minimal information about software versions and installed services.
6. Input Validation and Sanitization: Administrators should ensure that all user inputs are validated and sanitized to prevent injection attacks.^{20,21}
7. Only Use HTTPS: Administrators should strictly prohibit the use of HTTP (plaintext protocols).

The sixth test case is very similar to the third test case when it comes to mitigation strategies.

The seventh test case deals with the application vulnerabilities. Cross-Site Scripting (XSS) is a vulnerability that allows attackers to inject malicious scripts into content that other users see and interact with. Cross-Site Request Forgery (CSRF), also known as XSRF, is an attack that tricks the victim into submitting a malicious request.^{20,22} Usually, XSRF is done in conjunction with CSRF discussed above. This can lead to unauthorized commands being transmitted from a user that the web application trusts.

Mitigation strategies for XSS include:

1. Sanitizing user input to ensure that the input is not malicious code.
2. Employing Content Security Policy (CSP) headers.

For CSRF, mitigation techniques include:

1. Using anti-CSRF tokens in forms that change server state.
2. Implementing same-site cookies to restrict cookies to first-party contexts.
3. Verifying the HTTP `Referer` header for requests to ensure they originate from trusted sources.

The last test case deals with internal threats that can exploit inherent network vulnerability known as ARP spoofing. The mitigation techniques include:

1. Static ARP Entries: Administrators should configure devices to use static ARP entries for critical devices to prevent ARP spoofing.
2. ARP Spoofing Detection Tools: For larger networks, administrators should deploy tools designed to detect ARP spoofing.
3. Dynamic ARP Inspection (DAI): This allows the administrators to inspect ARP packets on the network and block the potentially suspicious ones.
4. Network Segmentation: Lastly, the administrators should divide the network into smaller, isolated segments.

The role of regulatory bodies and industry standards is pivotal in shaping the security landscape of IoMT. While the EU has passed the GDPR regulation with a specific emphasis on protecting the patient data, the regulations do not mandate controls that are binding on the technology providers.²³ Similarly, the US has put many requirements on patient health data via HIPAA but is unclear regarding the mandatory controls and safeguards.²⁴ Furthermore, the NIST SP 800 guidelines are not binding on technology providers but rather merely provide a recommendation regarding controls. The rapid innovation in the technology realm introduces new attack vectors that need to be addressed by the regulatory bodies.

CONCLUSION

Healthcare providers and technology implementors are striving to provide solutions that would allow better healthcare options for the patients. This combination, however, lacks in-depth awareness of potential risks that are being introduced to the healthcare ecosystem. Such risks can significantly compromise patient safety and data privacy. The study at hand has shed light on several critical issues, including the use of outdated software, poor user awareness, and inadequate monitoring/choice of tool deployment. It is imperative that a proactive approach to IoMT security is put in place and

stakeholders should delve in continuous monitoring and improvement.

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REFERENCES

1. Rajput A, Brahimi T. Characterizing internet of medical things/personal area networks landscape. In *Innovation Health Informatics* 2020 Jan 1:353-371.
2. Piantadosi V, Scalabrino S, Oliveto R. Fixing of security vulnerabilities in open-source projects: A case study of apache http server and apache tomcat. In *2019 12th IEEE Conference on software testing, validation and verification (ICST)* 2019;Apr 22 (pp. 68-78). IEEE.
3. Rajput A, Rotenstreich S. Making A Case for Resource Management in a P2P Environment. In *IKE*; 2004 (pp. 475-484).
4. O'Leary M, O'Leary M. Privilege Escalation in Linux. *Cyber Operations: Building, Defending, and Attacking Modern Computer Networks*. 2019; (pp. 419-453).
5. Ahmed S. Byod, personal area networks (PANs) and IOT: threats to Patients Privacy. In *Research & Innovation Forum 2019: Technology, Innovation, Education, and their Social Impact 1* 2019; (pp. 403-410). Springer International Publishing.
6. Thierer A, Castillo A. Projecting the growth and economic impact of the internet of things. *George Mason University, Mercatus Center*, June. 2015.
7. Rajput AE, Ahmed SM. Big data and social/medical sciences: state of the art and future trends. *arXiv preprint arXiv:1902.00705*. 2019 Feb 2.
8. Bartlett J. *Building Scalable PHP Web Applications Using the Cloud: A Simple Guide to Programming and Administering Cloud-Based Applications*. Apress; 2019 Nov 27.
9. Ahmed S, Rajput AE, Sarirete A, Aljaberi A, Alghanem O, Alsheraigi A. Studying unemployment effects on mental health: social media versus the traditional approach. *Sustainability* 2020;12:8130-6.
10. Westfall J, Westfall J. *Basics of Linux security. Set Up and Manage Your Virtual Private Server: Making System Administration Accessible to Professionals*. 2021:111-31.
11. Huang J, Li Y, Zhang J, Dai R. U Checker: Automatically detecting php-based unrestricted file upload vulnerabilities. In *2019 49th Annual IEEE/IFIP International Conference on Dependable Systems and Networks (DSN)* 2019;24:581-592.
12. Pooj K, Patil S. Understanding File Upload Security for

- Web Applications. *International J Engineering Trends Technol* 2016;42:342-347.
13. Mehanna N, Rudametkin W, Laperdrix P, Vastel A. Free Proxies Unmasked: A Vulnerability and Longitudinal Analysis of Free Proxy Services. *arXiv preprint arXiv:2403.02445*. 2024 Mar 4.
14. Sabetta A, Ponta SE, Lozoya RC, Bezzi M, Sacchetti T, Greco M, et al. Known Vulnerabilities of Open Source Projects: Where Are the Fixes? *IEEE Security & Privacy*. 2024 Jan 5.
15. Lincke S. Understanding Software Threats and Vulnerabilities. In *Information Security Planning: A Practical Approach* 2024, pp. 381-400. Cham: Springer International Publishing.
16. Alrawais A, Alhothaily A, Hu C, Cheng X. Fog computing for the internet of things: Security and privacy issues. *IEEE Internet Computing* 2017;21:34-42.
17. Ahmed SM, Rajput A. Threats to patients' privacy in smart healthcare environment. In *Innovation in Health Informatics* 2020 (pp. 375-393). Academic Press.
18. Wirzenius L, Oja J, Stafford S, Weeks A. The Linux System Administrator's Guide. Version 0.6. 1993;2.
19. Aladi CC. Web Application Security: A Pragmatic Exposé. *Digital Threats: Research and Practice*. 2024.
20. Sambhus K, Liu Y. Automating SQL Injection and Cross-Site Scripting Vulnerability Remediation in Code. *Software* 2024;3:28-46.
21. Khodayari S, Barber T, Pellegrino G. The Great Request Robbery: An Empirical Study of Client-side Request Hijacking Vulnerabilities on the Web. In *Proceedings of 45th IEEE Symposium on Security and Privacy*, 2024.
22. Wilson G, Weidner K, Salem L. Extending Linux for multi-level security. In *security Enhanced Linux Symposium* 2007 Mar.
23. Dunn Cavelty M, Smeets M. Regulatory cybersecurity governance in the making: The formation of ENISA and its struggle for epistemic authority. *J Eur Public Policy* 2023;30:1330-52.
24. Kelly B, Quinn C, Lawlor A, Killeen R, Burrell J. Cybersecurity in Healthcare. *Trends of Artificial Intelligence and Big Data for E-Health*. 2023 Jan 2:213-31.

Effects of mobilization with movement and Maitland grade III mobilization on pain and physical function in plantar fasciitis

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Objective: To determine the effects of mobilization with movement and Maitland grade III mobilization on pain and physical function in plantar fasciitis.

Methodology: This randomized clinical trial used convenient sampling. The sample size was 16. Patients were assigned randomly in group A and group B by computer-generated random number table. The group A was treated with mobilization with movement, gastrocnemius stretching, stretching of plantar fascia and ultrasound therapy. The group B was treated with Maitland grade III mobilization, gastrocnemius stretching, stretching of plantar fascia and ultrasound therapy. The treatment was given for a total of 4 weeks

two sessions each week. NPRS and FAAM were used for measuring pain and physical function. The outcome measure was recorded at baseline and after 4 weeks.

Results: The difference between the two groups was not statistically significant ($p>0.05$). The difference within a group was statistically significant and shown an improvement ($p<0.05$).

Conclusion: Mobilization with movement and Maitland grade III mobilization were equally effective for reducing pain and improving physical function in plantar fasciitis.

Keywords: Fasciitis, plantar, sitting position, pain.

INTRODUCTION

Plantar fasciitis (PF) is a common reason of pain in heel.¹ Pain is aggravated in the morning and increases at the start of the walk.² The fascia of the foot is a thick focal area which overlay focal muscles of the primary surface which include “flexor digitorum brevis” and is situated directly deep to the external surface of the plantar fascia.³ Many different interventions exist to manage PF.⁴ Mobilization is an effective choice to reduce pain and dysfunction. Activities of daily living are reduced in PF because the range of ankle joint is decreased. Mulligan’s MWM intervention is very effective in reducing the pain.⁵ Manual therapy includes the mobilization of the subtalar joint combine with stretching and ultrasound.⁶ Self-soft tissue massage by the help of ball of tennis and foam roller both show improvement.⁷ Trigger point release technique gives better results than muscle energy technique in chronic patients.⁸

To the best of our knowledge, comparison of mobilization with movement and Maitland grade III mobilization in patients with PF has not addressed yet. The purpose of the present study was to compare two different modalities of manual therapy on patients with PF such as mobilization with movement and Maitland grade III mobilization.

METHODOLOGY

This randomized single-blinded clinical trial was

conducted at Riphah Rehabilitation Center. It was registered in WHO trial registry IRCT (Registration # IRCT20200218046541N1) and approved by Riphah Ethical Committee (REC/RCRS/20/1032) and BASR. An informed written consent was taken from all patients. Sample size was calculated by G Power software 3.1.9.2 version with the power of study .80 and a margin of error 5%.⁵ Sample was taken of 16 by the 10% attrition rate and with 8 patients in each group by computer-generated random number table.

Inclusion criteria were age 30-60 years, both gender patients with chronic PF (unilateral), tender medial side of the calcaneus on palpation, pain on insertion of the plantar fascia by palpation, pain on weight-bearing activities, positive results of windlass test and negative results of tarsal tunnel test. Exclusion criteria were patient having any arthritis such as rheumatoid arthritis, reactive arthritis, tumor, fracture of tarsals and metatarsals, tarsal tunnel syndrome and any recent surgery of ankle and foot. Convenient sampling technique was used.

Intervention of group A was mobilization with movement, gastrocnemius stretching, stretching of plantar fascia and ultrasound therapy. Intervention of group B was Maitland grade III mobilization, gastrocnemius stretching, stretching of plantar fascia and ultrasound Therapy.⁹⁻¹⁴ The treatment was given for a total of 4 weeks, two sessions each week. The outcome was measured at baseline and after 4 weeks 17. Numeric

pain rating scale (NPRS) was used for measuring pain. Foot and ankle ability measure (FAAM) was used for measuring physical function.

Statistical Analysis: Data were analyzed through SPSS version 21. After testing the normality by Shapiro-wilk test, parametric test was used in between and within group analysis. For between group analysis, independent sample t-test was used. For within group analysis paired sample t-test was used. $p < 0.05$ was considered significant.

RESULTS

Demographic characteristics are shown in Table 1. p-values of both groups were similar. Between group comparison of NPRS and FAAM is shown in Table 2. p-value between two groups was not statistically significant. Both groups were equally effective based on p value. Within group comparison of NPRS and FAAM is shown in Table 3.

Between group comparison of NPRS and FAAM is shown in Table 2. p-value between two groups was not statistically significant. Both groups were equally effective based on p value. Within group comparison of NPRS and FAAM is shown in Table 3.

DISCUSSION

Our study evaluated the effects of mobilization with movement and Maitland grade III mobilization on pain and physical function in PF. Muneer et al, reported that mobilization improved dorsiflexion of ankle and relieved pain.⁵ Our study found the mobilization with movement and Maitland grade III mobilization were equally effective for reducing pain and improving physical function in PF. In the present study, MWM also relieved pain and improved physical function.

Celik et al compared joint mobilization + stretching and injection of steroid for the management of PF and found that both groups showed improvement at follow up of 3, 6 and 12 weeks. The prominent betterment proceeds in just the mobilization +stretching group for a while extending from 12 weeks to 1 year.¹¹ Our follow-up was short due to covid-19. Celik et al provided mobilization of grade I and grade II,¹¹ but the present study provided Maitland

Table 1: Comparison of age, weight, height and BMI of both groups.

Variable	Group A n=7 (Mean $\pm$ S.D)	Group B n=7 (Mean $\pm$ S.D)	p-value
Age (Years)	42.71 $\pm$ 7.95	42.28 $\pm$ 8.01	0.92
Weight(kg)	63.85 $\pm$ 9.20	66.00 $\pm$ 7.21	0.637
Height(cm)	162.55 $\pm$ 10.13	157.47 $\pm$ 8.79	0.336
BMI (Body Mass Index)	24.32 $\pm$ 4.10	26.68 $\pm$ 3.15	0.252

Table 2: Between group comparison of NPRS and FAAM.

Variable	Group A n=7	Group B n=7	p-value
Pre-Treatment NPRS Score (Mean $\pm$ S.D)	7.71 $\pm$ 1.11	8.00 $\pm$ 1.52	0.69
Post Treatment NPRS Score (Mean $\pm$ S.D)	1.14 $\pm$ 0.37	1.28 $\pm$ 0.48	0.55
Pre-Treatment FAAM Value (Mean $\pm$ S.D)	48.42 $\pm$ 15.74	46 $\pm$ 19.90	0.804
Post Treatment FAAM Value (Mean $\pm$ S.D)	90.14 $\pm$ 13.42	86.42 $\pm$ 10.90	0.580

Table 3: Within group comparison of NPRS and FAAM.

Variable	Group A n=7	Group B n=7
Pre-Treatment NPRS Score (Mean $\pm$ SD)	7.71 $\pm$ 1.11	8.00 $\pm$ 1.52
Post Treatment NPRS Score (Mean $\pm$ SD)	1.14 $\pm$ 0.37	1.28 $\pm$ 0.48
p-value	0.00	0.00
Pre-Treatment FAAM Value (Mean $\pm$ S.D)	48.42 $\pm$ 15.74	46.00 $\pm$ 19.90
Post Treatment FAAM Value (Mean $\pm$ S.D)	90.14 $\pm$ 13.42	86.42 $\pm$ 10.90
p-value	0.000	0.001

grade III mobilization and they also used VAS and FAAM, as we did.

Ghaffor et al, used LEFS, FAAM, NPRS to measure outcomes pain and performance and reported that conventional physical intervention with manual intervention and exercise was more effective than only

conventional intervention to manage the PF.¹⁵

Heggannavar et al, reported that combination of mobilization of subtalar joint+stretching+ultrasound was better than stretching and ultrasound alone.⁶ In the present study, mobilization also showed effectiveness in management of PF. They used VAS and FFI for measured outcomes. Heggannavar et al, sample size was 14.¹⁶ Our study sample was 16. They gave 6 treatment sessions in each week.⁶ In the present study, treatment was given for a total of 4 weeks, two sessions each week. Limitations of study was due to covid-19 we face the difficulty in recruitment of the patients. There is generalizability issue because male and female ratio are not equal.

CONCLUSION

Mobilization with movement and Maitland grade III mobilization were equally effective for reducing pain and improving physical function in plantar fasciitis.

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REFERENCES

1. Huffer D, Hing W, Newton R, Clair M. Strength training for plantar fasciitis and the intrinsic foot musculature: A systematic review. *Phys Ther Sport* 2017;24:44-52.
2. Fraser JJ, Glaviano NR, Hertel J. Utilization of physical therapy intervention among patients with plantar fasciitis in the United States. *J Orthop Sports Phys Ther* 2017;47:49-55.
3. Pawar PA, Tople RU, Yeole UL, Gharote GM, Panse RB, Kulkarni SA. A study on the effect of strain-counterstrain in plantar fasciitis. *Int J Adv Med* 2017;4:551-2.
4. Hansen L, Krogh TP, Ellingsen T, Bolvig L, Fredberg U. Long-term prognosis of plantar fasciitis: a 5-to 15-year follow-up study of 174 patients with ultrasound examination. *Orthop J Sports Med* 2018;6:2325967118757983.
5. Munir S, Babur MN, Sultana B, Kafeel S, Aslam H. Effectiveness of mulligan's mobilization techniques in the treatment of plantar fasciitis. *Int J Rehab Sci* 2018;7:7-9.
6. Heggannavar A, Gupta RK. Effectiveness of Subtalar Joint Mobilization in Plantar Heel Pain. *Ind J Physiother Occup Ther* 2015;9:75-9.
7. Hameed FS, Srivastava S. Effect of Self Myofascial Release Using Foam Roller Versus Tennis Ball in Subjects with Plantar Fasciitis: A Comparative Study. *Ind J Public Health Res Deve* 2020;11:474-8.
8. Sarkar B, Mangalam AK, Sahay P. Efficacy of muscle energy technique as compared to myofascial trigger point release in chronic plantar fasciitis: a double blind randomized clinical trial. *Int J Health Sci Res* 2018;8:128-36.
9. Mulligan BR. Manual Therapy: "nags", "snags", "mwms" Etc: Optp; 2004.
10. Maitland GD. Peripheral manipulation: Butterworth-Heinemann; 1977.
11. Celik D, Kuş G, Sırma SÖ. Joint mobilization and stretching exercise vs steroid injection in the treatment of plantar fasciitis: a randomized controlled study. *Foot Ankle Int* 2016;37:150-6.
12. Lin CC, Moseley AM, Refshauge KM, Haas M, Herbert RD. Effectiveness of joint mobilisation after cast immobilisation for ankle fracture: a protocol for a randomised controlled trial [ACTRN012605000143628]. *BMC Musculoskeletal Disord* 2006;7:46-9.
13. Green T, Refshauge K, Crosbie J, Adams R. A randomized controlled trial of a passive accessory joint mobilization on acute ankle inversion sprains. *Phys Ther* 2001;81:984-94.
14. Konjen N, Napnark T, Janchai S. A comparison of the effectiveness of radial extracorporeal shock wave therapy and ultrasound therapy in the treatment of chronic plantar fasciitis: a randomized controlled trial. *J Med Assoc Thai* 2015;98:S49-S56.
15. Ghafoor I, Ahmad A, Gondal JI. Effectiveness of routine physical therapy with and without manual therapy in treatment of plantar fasciitis. *Rawal Med J* 2016;41:2-6.

Ensuring accuracy of endotracheal tube placement by performing upper airway ultrasonography vs chest auscultation

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Objective: To determine the fastest technique (chest auscultation or upper airway ultrasonography) for confirming endotracheal tube placement in critically ill patients.

Methodology: This cross-sectional study included 110 critically ill patients of age >18 years who requires endotracheal intubation and were selected from emergency department of Ziauddin University Hospital (North Campus) Karachi by using non-probability consecutive sampling technique. 110 patients of ASA grade E were envaulted clinically and position of endotracheal tube was confirmed on chest auscultation (breath sounds presence) and upper airway ultrasonography (presence of lung sliding sign). Time required for both techniques was recorded.

Results: Endotracheal tube placement was 100.0% in

critically ill patients; of which male were 60.0% and female were 40.0% having mean age of 55.21±16.66 years. Respiratory failure (62.7%) was the most common presentation in critically ill patients followed by heart failure (16.4%), renal failure (16.4%), low Glasgow Coma Scale (GCS; 6.4%) and cerebrovascular accident (CVA; 4.5%). Endotracheal tube placement confirmation was more rapid in upper airway ultrasonography (7.40±2.31 seconds) as compared to chest auscultation (10.34±2.75 seconds).

Conclusion: Confirmation of endotracheal tube placement was faster with upper airway ultrasonography than with chest auscultation.

Keywords: Auscultation, ultrasonography, intubation, emergency.

INTRODUCTION

Critically ill patients are more likely to be hospitalized and require care in the emergency department.^{1,2} Emergency physicians are solely responsible for providing appropriate intensive care to critically ill patients,³ including clinical assessment, diagnostic investigations, lifesaving interventions and medications.^{3,4} Endotracheal intubation (ETI) is the most commonly used life-saving intervention for airway management of critically ill patients.⁵ However, this technique carries a significant risk of complications and requires highly skilled technicians for proper insertion of endotracheal tube (ETT). During ETI, approximately half of critically ill patients may experience life-threatening complications.^{5,6}

Some of the major complications of ETI include hypoxemia and cardiovascular complications, particularly hemodynamic collapse resulting in cardiac arrest, and death.⁷ Multiple attempts during ETI, misplaced (esophageal or right main-stem intubation) or failed ETI, poor oxygenation, nasal or upper airway trauma, laceration of oropharyngeal, vocal cords or trachea, tooth avulsion, aspiration, perforation, tracheal necrosis or stenosis and glottic edema are some of the

complications that arise during ETI.^{8,9} Therefore, ETT position should be assessed immediately after ETI by using reliable approaches.^{10,11}

In the emergency department, chest auscultation and bedside ultrasonography are commonly used to assess ETT position. Chest auscultation is an easy and efficient method which depends only on the skill of the physician and does not require any special equipment. However, its effectiveness may not always be reliable. In contrast, bedside ultrasonography is also a simple, efficient, and less invasive method of confirming the position of ETT. This is considered a more reliable and appropriate method for confirming the position of ETT.^{12,13} Therefore, this study aimed to determine the fastest technique (chest auscultation or upper airway ultrasonography) for confirming ETT placement in critically ill patients.

METHODOLOGY

This cross-sectional study was conducted at Emergency department (ED) of Ziauddin University Hospital, North Campus Karachi from 16-11-2021 to 15-05-2022. The study was approved by Research Committee and Ethics Committee (No: 000) of Ziauddin University Karachi and

written informed consent was also taken from the relatives of critically ill patients.

Critically ill patients of (1) both gender (2) age >18 years (3) need of ETI (4) ASA grade E and (5) with consent were selected from ED by using non-probability consecutive sampling technique. Patients of (1) age <18 years (2) severe neck trauma (3) history of neck surgery and (4) high risk of aspiration were excluded. Sample size of 110 was calculated by using online sample size calculator (<https://wnarifin.github.io/ssc/sssns.html>) and sensitivity of 97.0% and specificity of 71.4% of upper airway ultrasonography in placing ETT at correct position,¹⁴ by taking confidence interval of 95% and drop out of 10%.

Before ETI, a similar standard anesthetic protocol was followed. ETI was performed by an experienced emergency physician and position was confirmed by chest auscultation and upper airway ultrasonography (experienced sonographer). Time required to complete chest auscultation and upper airway ultrasonography was recorded.

Statistical Analysis: Data were analyzed using SPSS version 25. An independent sample t-test was used for comparing mean time of completion of chest auscultation and upper airway ultrasonography. $p \leq 0.05$ was used for confirming significance.

RESULTS

Out of 110 patients, 66 (60.0%) were male and 44 (40.0%) females. Most were elders with mean age of 55.21 ± 16.66 years and fall in age group of >50 years 67 (60.9%) patients (Table 1). Respiratory failure (62.7%) was the most common clinical presentation followed by heart failure (16.4%), renal failure (16.4%), low GCS (6.4%) and CVA (4.5%) (Fig. 1).

ETT placement was 100.0% in all patients. ETT placement confirmation was more rapid in upper airway ultrasonography (7.40 ± 2.31 seconds) as compared to chest auscultation (10.34 ± 2.75 seconds). Time to complete chest auscultation and upper airway ultrasonography was also distributed in groups; ≤ 10 seconds in 67 (60.9%) and 107 (97.3%) patients and >10 seconds in 43 (39.1%) and 3 (2.7%) patients (Table 2). The p-value on independent sample t-test was <0.001 and

Table 1: Baseline characteristics of critically ill patients (n=110).

Variable		Frequency	%
Gender	Male	66	60.0%
	Female	44	40.0%
Age (Years)	Mean $\pm$ SD	55.21 ± 16.66	
	≤ 50	43	39.1%
	> 50	67	60.9%
Vitals	Heart Rate (beats/min)	105.48 ± 27.27	
	Systolic Blood Pressure (mmHg)	127.17 ± 33.72	
	Diastolic Blood Pressure (mmHg)	81.48 ± 22.65	
	Oxygen Saturation (%)	84.95 ± 12.99	

Table 2: Time to complete chest auscultation and upper airway ultrasonography.

Time to Complete	Chest Auscultation	Ultrasonography	p-value
Mean ± SD	10.34 ± 2.75	7.40 ± 2.31	<0.001*
≤ 10 Seconds	67 (60.9%)	107 (97.3%)	0.028**
> 10 Seconds	43 (39.1%)	3 (2.7%)	
* Independent sample t-test. ** Chi-square test			

chi-square test was 0.028 indicating a significantly shorter time to detect the correct position of the ETT by

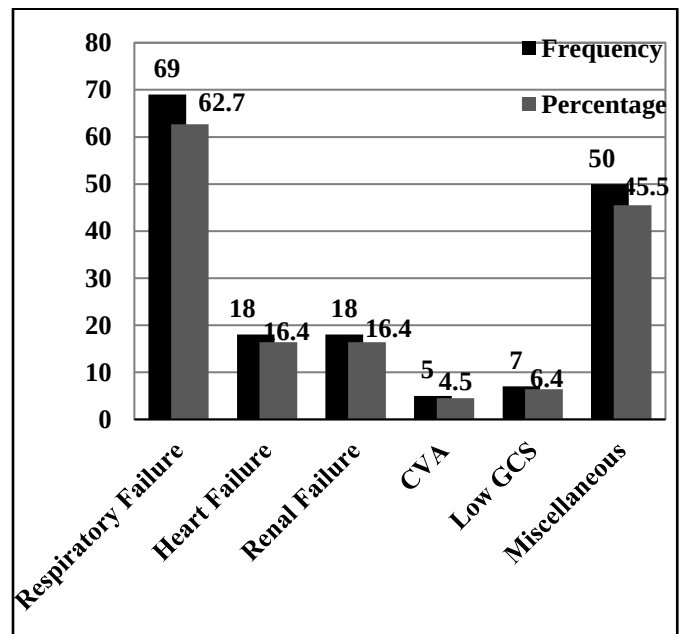


Fig. 1. Clinical presentation in critically ill patients.

using upper airway ultrasonography as compared to chest auscultation.

DISCUSSION

The words “critical illness” and “critical care” are commonly used in the emergency department. In most EDs, the term critical illness is used for patients’ overall health and critical care for management of critically ill patients.^{15,16} Therefore, emergency physicians should focus on providing critical care through airway management to reduce the risk of complications, morbidity as well as mortality.^{17,18} One of the major issues for physicians of ED is the appropriate placement of ETTs. ETT position should be assessed immediately by using reliable approaches.

One hundred and ten critically ill patients participated in the study; of which male patients were 66 (60.0%) and female patients were 44 (40.0%). Similar studies are reporting that male patients are more likely to have critical illnesses and require airway management by ETI such as Arafa et al, reports 63.6% male patients,¹⁴ Bansal reports 53.6% male patients,¹⁹ Rajan et al, reports 52.5% male patients,²⁰ Thomas et al, reports 59.0% male patients,²¹ and Abdelrahman et al, reports 60.0% male patients.²²

In this study, most patients were elders with mean age of 55.21 ± 16.66 years. Similar studies are reporting differences in the mean age of patients due to differences in the selection of patient age groups for the study such as; Arafa et al,¹⁴ reports most of the patients (70.5%) in age group of <50 years and only 29.5% patients in age group of >50 years,¹⁴ Bansal also reports a lower mean age of 35-38 years,¹⁹ Rajan et al,²⁰ reports the mean age of 32.9 and 50.6 years in patients with BMI of <25 and >25 Kg/m² Thomas et al,²¹ reports higher mean age of 50.79 ± 16.15 years, and Abdelrahman et al, also report higher mean age of 50 years.²²

The diagnostic accuracy and sensitivity of both methods was 100.0%. Similar studies are reporting higher diagnostic accuracy and sensitivity with chest auscultation and upper airway ultrasonography such as; Arafa et al. reports the diagnostic accuracy of 88.8% and 95.3% and sensitivity of 93.6% and 97.0% in chest auscultation and in upper airway ultrasonography respectively,¹⁴ Bansal reports the 98.5% diagnostic accuracy and 97.0% sensitivity of upper airway ultrasonography,¹⁹ Thomas et al, reports the 97.9% sensitivity of upper airway ultrasonography,²¹ and Abdelrahman et al, report the 91.4% diagnostic accuracy and 93.8% sensitivity of upper airway ultrasonography.²² The p-value on independent sample t-test was <0.001 and chi-square test was 0.028 indicating a significantly shorter time to detect the correct position of the ETT by

using upper airway ultrasonography as compared to chest auscultation. Similar studies are reporting a lower mean time to confirm ETT position with upper airway ultrasonography than chest auscultation such as; Rajan et al, report the lower mean time (8.57 ± 2.05 vs. 8.61 ± 1.66 seconds) with upper airway ultrasonography and higher mean time (9.34 ± 2.43 vs. 14.35 ± 5.53 seconds) with chest auscultation in patients with BMI of <25 and >25 Kg/m² respectively,²⁰ and Thomas et al, also report the lower mean time (8.27 ± 1.54 seconds) with upper airway ultrasonography and higher mean time (20.72 ± 3.21 seconds) with chest auscultation.²¹ In contrast, Arafa et al, report the lower mean time (11.14 ± 1.3 seconds) with chest auscultation and higher mean time (13.5 ± 2.15 seconds) with upper airway ultrasonography.¹⁴

CONCLUSION

Both upper airway ultrasonography and chest auscultation are simple, quick, effective, and accurate procedures with many advantages and few disadvantages including need for trained personnel in upper airway ultrasonography’s and difficulty in determining the depth of ETT in chest auscultation. These obstacles can be easily overcome and both methods can be effectively used for ETT confirmation. Confirmation of ETT placement was faster with upper airway ultrasonography than with chest auscultation.

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REFERENCES

1. Lin S, Ge S, He W, Zeng M. Association of delayed time in the emergency department with the clinical outcomes for critically ill patients. *QJM Int J Med* 2021;114:311-7.
2. Bernhard M, Döll S, Kramer A, Weidhase L, Hartwig T, Petros S, et al. Elevated admission lactate levels in the emergency department are associated with increased 30-day mortality in non-trauma critically ill patients. *Scand J Trauma Resusc Emerg Med* 2020;28:1-8.
3. Jeong H, Jung YS, Suh GJ, Kwon WY, Kim KS, Kim T, et al. Emergency physician-based intensive care unit for

- critically ill patients visiting emergency department. *Am J Emerg Med* 2020;38:2277-82.
4. Gunnerson KJ, Bassin BS, Havey RA, Haas NL, Sozener CB, Medlin RP, et al. Association of an emergency department-based intensive care unit with survival and inpatient intensive care unit admissions. *JAMA Netw Open* 2019;2:e197584.
5. Cabrini L, Landoni G, Baiardo Redaelli M, Saleh O, Votta CD, Fominskiy E, et al. Tracheal intubation in critically ill patients: a comprehensive systematic review of randomized trials. *Crit Care* 2018;22:1-9.
6. Mosier JM, Sakles JC, Law JA, Brown III CA, Brindley PG. Tracheal intubation in the critically ill. Where we came from and where we should go. *Am J Respir Crit Care Med* 2020;201:775-88.
7. Alvarado AC, Panakos P. Endotracheal Tube Intubation Techniques. [Updated 2023 Jul 10]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan.
8. Ji C, Ni Q, Chen W. Diagnostic accuracy of radiology (CT, X-ray, US) for predicting difficult intubation in adults: a meta-analysis. *J Clin Anesth* 2018;45:79-87.
9. Smischney N, Kashyap R, Seisa M, Schroeder D, Diedrich D. Endotracheal intubation among the critically ill: protocol for a multicenter, observational, prospective study. *JMIR Res Protoc* 2018;7:e11101.
10. Higgs A, McGrath BA, Goddard C, Rangasami J, Suntharalingam G, Gale R, et al. Guidelines for the management of tracheal intubation in critically ill adults. *Br J Anesth* 2018;120:323-52.
11. Ghatehorde NK, Regunath H. Intubation Endotracheal Tube Medications. [Updated 2023 May 5]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan.
12. Natt B, Mosier J. Airway management in the critically ill patient. *Curr Anesthesiol Rep* 2021;11:116-27.
13. Gottlieb M, Holladay D, Peksa GD. Ultrasonography for the confirmation of endotracheal tube intubation: a systematic review and meta-analysis. *Ann Emerg Med* 2018;72:627-36.
14. Arafa S, Abouzkry A, Mohamady A. Accuracy of bedside upper airway ultrasonography vs standard auscultation for assuring the location of endotracheal tube after tracheal intubation: comparative study controlled by quantitative waveform capnography. *J Anesth Clin Res* 2017;9:1000804.
15. Schell CO, Gerdin Wärnberg M, Hvarfner A, Höög A, Baker U, Castegren M, et al. The global need for essential emergencies and critical care. *Crit Care* 2018;22:284.
16. Kayambankadzanja RK, Schell CO, Wärnberg MG, Tamras T, Mollazadegan H, Holmberg M, et al. Towards definitions of critical illness and critical care using concept analysis. *BMJ Open* 2022;12:e060972.
17. Zhang S, Lin J, Diao X, Shi W, Huang L. Airway management in adult intensive care units: a survey of two regions in China. *BioMed Res Int* 2022;2022.
18. Admass BA, Endalew NS, Tawye HY, Melesse DY, Workie MM, Filatie TD. Evidence-based airway management protocol for a critical ill patient in medical intensive care unit: Systematic review. *Ann Med Surg* 2022;104284.
19. Bansal P. Comparison of upper airway ultrasonography with standard waveform capnography and auscultation to verify correct placement of endotracheal tube after intubation. *Int J Contemp Med Res* 2018;5:11-5.
20. Rajan S, Surendran J, Paul J, Kumar L. Rapidity, and efficacy of ultrasonographic sliding lung sign and auscultation in confirming endotracheal intubation in overweight and obese patients. *Indian J Anaesth* 2017;61:230-4.
21. Thomas VK, Paul C, Rajeev PC, Palatty BU. Reliability of ultrasonography in confirming endotracheal tube placement in an emergency setting. *Indian J Crit Care Med* 2017;21:257-61.
22. Abdelrahman TN, Abdelhameed GA, Armanious SH. Evaluation of real-time tracheal ultrasound versus colorimetric capnography as a point of care tool for confirmation of endotracheal intubation: a randomized controlled study. *Ain Shams J Anesthesiol* 2020;12:1-8.

Factors affecting adherence to medical nutrition therapy and physical activity among people with type 2 diabetes

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Objective: To assess different factors affecting adherence to medical nutrition therapy and physical activity among people with type 2 diabetes.

Methodology: This cross-sectional study was conducted at Baqai Institute of Diabetology and Endocrinology, Karachi, Pakistan from November 2018 till March 2019. Patients with type 2 diabetes who got physical activity and dietary advice previously at least once were included. Data were collected by a dietitian on one-to-one basis by a self-structured questionnaire.

Results: Out of 385 patients, 192 were males and 193 females. Among them, 60% were compliant to dietary advice whereas only 44.2% were compliant to physical activity. Common reasons related to non-compliance with diet were lack of self-care in 35.7%, don't like recommended food in 34.4%, don't remember the

recommended diet in 31.2% and difficult to get healthy food in 25.3%. The most common reasons for non-compliance with exercise were don't remember to do physical activity in 83.7% followed by lack of will power/motivation in 71.5%, pain in legs in 60% and family responsibilities in 23.8%. Last counselling within preceding 2 years, <5 years duration of diabetes was associated statistically significant with dietary compliance. Patients who were compliant to diet were also doing physical activity ($p=0.000$).

Conclusion: It is necessary to address the specific and individual reasons for noncompliance of diet and exercise and provide appropriate solutions to achieve good glycemic control.

Keywords: Compliance, medical nutrition therapy, physical activity, type 2 diabetes.

INTRODUCTION

The prevalence of type 2 diabetes (T2DM) has increased globally, and Pakistan ranks 3rd in the world.¹ Type 2 diabetes management requires high cost causing huge burden on health care system and due to improper management, quality of life is affected along with several complications.² The management includes pharmacotherapy along with important changes in the lifestyle like healthy eating habits and consistent physical activities. The diabetes prevention program (DPP) states that changes in diet and physical activity may create a 5-8% weight loss resulting in good glycemic control.³ Moreover consistency in lifestyle modification reduces the risk of diabetes related complications.⁴

To bring change in the lifestyle is one of the most difficult and challenging part of the treatment.⁵ Compliance has been described as the degree to which an individual's actions taking medicine, following dietary and exercise advice correctly from a health care professional.⁶ There are certain factors that are a cause for no compliance to dietary recommendations such as socioeconomic position, duration of diabetes, lack of diabetes management information, affordability of a healthy diet and infrequent communication with healthcare professionals.⁷ The aim of this study was to determine

reasons and barriers of noncompliance related to medical nutrition therapy and physical activity among Pakistani patients with T2DM.

METHODOLOGY

This cross-sectional study was conducted at Baqai Institute of Diabetology and Endocrinology (BIDE) a tertiary care diabetes center in Karachi, Pakistan from November 2018 to March 2019. Ethical approval was obtained from the IRB of BIDE (Ref: BIDE/IRB/TRASHID/08/20/20/0241). Patients with T2DM, ≥ 20 years of age, irrespective of gender, who got at least one counseling session regarding dietary advice from dietitians and also counselled to do physical activity for 150 minutes per week attending the outpatient department of BIDE were included. Those with type 1 diabetes, pregnant females, newly diagnosed T2DM (<6 months duration) and patients with serious complications were excluded from the study.

Baseline characteristics (age, weight, height, body mass index (BMI), duration of diabetes, glycemic control through self-monitoring of blood glucose (SMBG) charts and HbA1C), their dietary choices and calorie requirement were collected through health management system (HMS) of BIDE. HMS is an integrated software

system that records patient's relevant data. Data were collected after taking informed consent.

A self-structured questionnaire was prepared by reviewing the literature. Each participant's dietary intake from all food groups and usual calories intake was recorded and compared with individual's calories requirement. Reasons of noncompliance to diet and physical activity were also asked from each participant and recorded.

Patient was considered dietary compliant if he/she was doing below mentioned ≥ 2 things on ≥ 4 days a week.⁸ Proper distribution of carbohydrates over various meals of the day. (Within their calories ranges). Taking appropriate number of calories within 10% of their requirement range. Taking balanced diet on most of the days of the week. (Balance diet means taking appropriate number of portions from all the food groups within their calorie requirement.) Physical activity was considered compliant if doing ≥ 150 minutes of moderate physical activity per week like walking, swimming, gardening, etc.⁹

Statistical Analysis: SPSS version 21 was used for data analysis. $p < 0.05$ was considered significant.

RESULTS

A total of 385 people (192 males and 193 females) were included in the study. Mean age was 53.0 ± 11.2 years. Demographic features are shown in Table 1. More patients were diet compliant than physical activity (Fig. 1). Lack of self-care and don't like recommended foods were commonest reasons for noncompliance of dietary advice (Fig. 2). Don't remember and lack of motivation were commonest factors in noncompliance for physical activity (Fig. 3).

Table 1: Basic characteristics (N=385).

Variables	Number (%)
Age (years)	53.07 ± 11.29
Gender	
Male	192(49.9%)
Female	193(50.1%)
Ethnicity	
Urdu	257(66.8%)
Punjabi	13(3.4%)
Sindhi	34(8.8%)
Pushto	71(18.4%)
Memon	10(2.6%)

Marital status	
Unmarried	7(1.8%)
Married	378(98.2%)
Occupation	
Housewife	165(42.9%)
Seat bound	162(42.1%)
Manual	14(3.6%)
Notworking/retired	44(11.4%)
Education	
No	97(25.2%)
Below matric	56(14.5%)
Matric	78(20.3%)
Graduate	115(29.9%)
Masters	39(10.1%)
Duration of DM	
< 5 years	150(39%)
5 to 10 years	104(27%)
>10 years	131(34%)
Last counselling	
≥ 2 years	167(43.4%)
<2 years	218(56.6%)
Taking calories within 10% of their requirements	
Excess	121(31.4%)
Control	264(68.6%)
Taking balance diet on most days	
No	145(37.7%)
Yes	240(62.3%)
Carbohydrates choices division daily	
No	186(48.3%)
Yes	199(51.7%)

Participants having less than 5 years duration of diabetes and who received their last dietary counselling within preceding two years were more adherent to dietary advice and physical activity ($p < 0.003$, $p < 0.0001$). Controlled carb amount, balance diet and meal spacing were also found statistically significant ($p < 0.0001$). Age, gender, marital status, education, occupation, and ethnicity were not found to be significantly associated.

DISCUSSION

This study showed that more than half of study participants were compliant to medical nutrition therapy and almost 2/5th compliant to physical activity. Participants having less than 5 years duration of diabetes and who received their last dietary counseling within the preceding two years were more adherent to dietary advice and physical activity. Those who are compliant to diet were also doing physical activity.

In our study, compliance to MNT is relatively much higher as compared to local studies done in Islamabad and Multan that showed only 1/3rd, 1/4th compliance rates, respectively.^{10,11} A study from Nepal revealed 87.5% study participants were non-adherent to dietary advice.⁴ The main reason for this discrepancy may be due to education regarding medical nutrition therapy. Another study from Nepal showed only 35% compliance with diet and exercise.¹² A study from Islamabad reported that people don't follow dietary advice due to unawareness

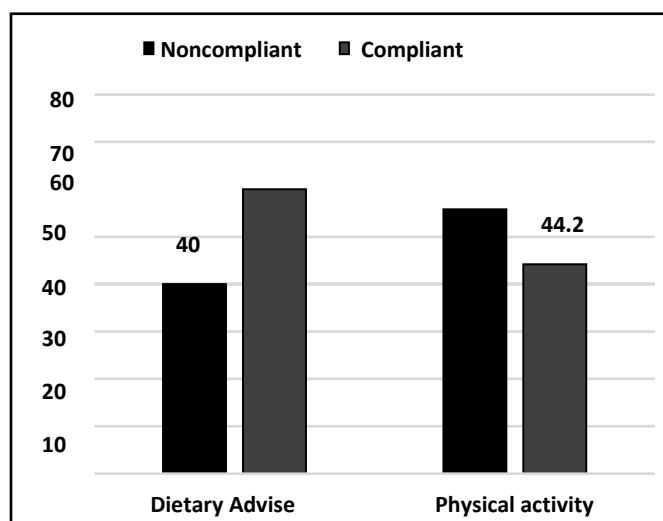


Fig. 1: Frequency of dietary and physical activity compliant.

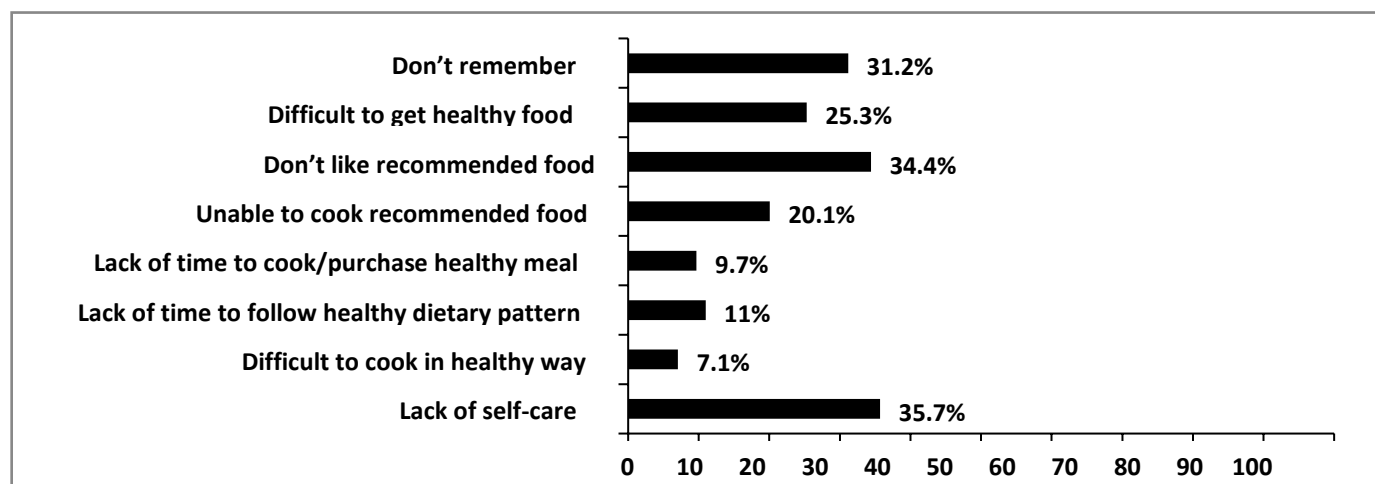


Fig. 2: Reasons for non-compliance to dietary advice.

and unavailability of counselling sessions.¹⁰ Another Pakistan study observed that majority of people feel difficulty in behavior change.¹³ Same reasons of non-compliance were found in the study from Ethiopia.¹⁵ Therefore it is imperative to counsel patients with family members.

Compliance rate with physical activity was found very low. A systemic review of barriers and facilitators for T2DM in South Asians had the same results.¹⁴ In our study, the most common reasons for non-compliance to exercise were don't remember followed by lack of will power/motivation, pain in legs,

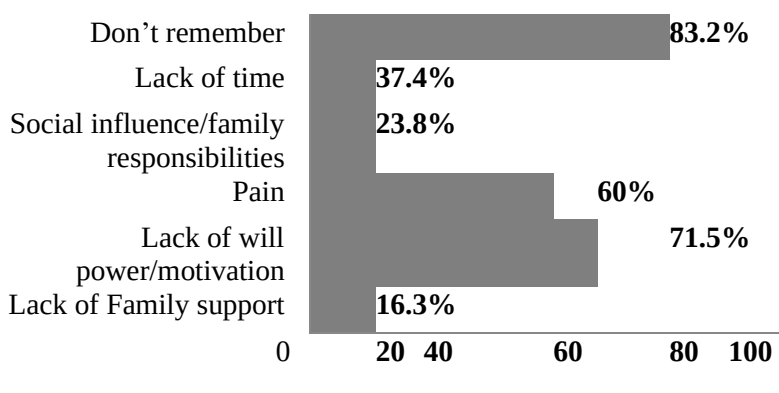


Fig. 3: Reasons for non-compliance to physical activity.

lack of time, social influence/family responsibilities and lack of family support. A study from Ethiopia showed the

most prominent reason was also lack of will power.¹⁵ Studies from Ethiopia,¹⁵ and Yemen,¹⁶ showed same results. Patients who received their last dietary counselling within the preceding two years were compliant to dietary advice. Hence, patients need continuous counselling sessions regarding behavior change. Lack of follow-ups and lack of motivation were main reasons for non-compliance. People with diabetes as having chronic nature of disease needs continuous reinforcement, motivation.¹⁷ Males from Basra, Iraq were more compliant to physical activity.¹⁸

In our study, those participants who regularly attended dietary and physical activity follow up visits were more compliant. A study from Saudi Arabia reported that irregularity of the follow up was one of the reason of non-compliance.⁵ One local study found that only 1/3 patients consulted their physicians for follow ups.¹³ A meta-analysis also concluded that there is a worldwide problem of lack of follow up visits among diabetic patients.¹⁹ Regular periodic counselling sessions must be done to improve behaviors and to manage day to day obstacles in regarding compliance.²⁰ Single centered study with already well-established education facility in regard to diet and physical activity are the main limitations. Furthermore, compliance assessment may be affected by recall bias.

CONCLUSION

Identification of factors responsible for noncompliance with dietary and lifestyle modifications is imperative for proper management of diabetes. It is necessary to address the specific and individual reasons for noncompliance to achieve good glycemic control. Periodic counselling positively reinforces the ability to adapt and maintain a healthy lifestyle.

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REFERENCES

- Sun H, Saeedi P, Karuranga S, Pinkepank M, Ogurtsova K, Duncan BB, et al. IDF Diabetes Atlas: Global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. *Diab Res Clin Pract* 2022;183:109119.
- Wu Y, Ding Y, Tanaka Y, Zhang W. Risk factors contributing to type 2 diabetes and recent advances in the treatment and prevention. *Int J Med Sci* 2014;11:1185.
- Ratner RE. Diabetes Prevention Program Research Group. An update on the diabetes prevention program. *Endoc Pract* 2006;12:20-4.
- Parajuli J, Saleh F, Thapa N, Ali L. Factors associated with nonadherence to diet and physical activity among Nepalese type 2 diabetes patients: a cross sectional study. *BMC Res Notes* 2014;7:1-9.
- Khan AR, Lateef ZN, Al Aithan MA, Bu-Khamseen MA, Al Ibrahim I, Khan SA. Factors contributing to non-compliance among diabetics attending primary health centers in the Al Hasa district of Saudi Arabia. *J Fam Comm Med* 2012;19:26.
- Garcia-Perez LE, Álvarez M, Dilla T, Gil-Guillén V, Orozco-Beltrán D. Adherence to therapies in patients with type 2 diabetes. *Diab Ther* 2013;4:175-94.
- Ayele AA, Emiru YK, Tiruneh SA, Ayele BA, Gebremariam AD, Tegegn HG. Level of adherence to dietary recommendations and barriers among type 2 diabetic patients: a cross-sectional study in an Ethiopian hospital. *Clin Diab Endocrinol* 2018;4:1-7.
- Early KB, Stanley K. Position of the Academy of Nutrition and Dietetics: the role of medical nutrition therapy and registered dietitian nutritionists in the prevention and treatment of prediabetes and type 2 diabetes. *J Acad Nutr Diet* 2018;11:8343-53.
- American Diabetes Association Professional Practice Committee, American Diabetes Association Professional Practice Committee:3. Prevention or delay of type 2 diabetes and associated comorbidities: Standards of Medical Care in Diabetes—2022. *Diab Care* 2022;45:39-45.
- Farooq MU, Mushtaq F, Naeem Z, Iqbal S, Naseem S, Ishtiaq O. Dietary habits and practices of type-2 diabetic patients in a tertiary care centre of Islamabad, Pakistan. *J Pak Med Assoc* 2018;68:825-30.
- Imtiaz S, Ullah H, Rasool MF, Hashmat F, Saleem M, Khan N. Assessment of compliance of diabetic patients at Nishtar hospital Multan, Pakistan. *Gomal J Med Sci* 2014;12:1-5.
- Ghimire S. Barriers to diet and exercise among Nepalese type 2 diabetic patients. *Int Schol Res Note* 2017;2017.
- Javed A, Mehmood A, Victor S, Haque Z. Attitudes, and behavior of adult Pakistani diabetic population towards their disease. *J Dow Univ Health Sci* 2014;8:89-93.
- Sohal T, Sohal P, King-Shier KM, Khan NA. Barriers, and facilitators for type-2 diabetes management in South Asians: a systematic review. *PloS one* 2015;10:e0136202.
- Zelege Negera G, Charles Epiphany D. Prevalence, and predictors of nonadherence to diet and physical activity recommendations among type 2 diabetes patients in Southwest Ethiopia: a cross-sectional study. *Int J Endocrinol* 2020;2020.

16. Alhariri A, Daud F, Almaiman A, Saghir S. Factors associated with adherence to diet and exercise among type 2 diabetes patients in Hodeidah city, Yemen. *Life* 2017;7:264-71.
17. Krishnan D, Gururajan R, Hafeez-Baig A, Kondalasamy-Chennakesavan S, Wickramasinghe N, Gururajan R. The impact of diet counselling on Type 2 Diabetes Mellitus: An Indian case study. *J Diab Metab* 2015;6. doi.org/10.4172/2155-6156.1000610
18. Aladhab RA, Alabbod MH. Adherence of patients with diabetes to a lifestyle advice and management plan in Basra, Southern Iraq. *Int J Diab Metab* 2019;25:61-6.
19. Lee RR, Mas'uud Ibnu Samsudin TT, Low LL, Kwan YH. Factors affecting follow-up non-attendance in patients with type 2 diabetes mellitus and hypertension: a systematic review. *Sing Med J* 2019;60:216-9.
20. Yang YJ. An overview of current physical activity recommendations in primary care. *Korean J Fam Med* 2019;40:135-9.

Frequency of mild cognitive impairments and its association with functional outcomes in stroke

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Objective: To determine the frequency of mild cognitive impairments and its association with functional outcomes in stroke.

Methodology: This cross-sectional study included 300 stroke patients of different hospitals among twin cities of Pakistan. Non-probability convenience sampling technique was used. Study included both male and female post stroke 1-week patients. A semi structured questionnaire was used along with Montreal cognitive assessment (MoCA) scale, Barthel Index and Lawton scale. Data analysis was performed by SPSS 21.

Results: Total sample size 300 with mean age of 57.88 ± 14.1 years. 241 patients had infarct stroke and 59 hemorrhagic stroke. 153 patients had right hemiplegia and 147 left hemiplegia. Mean MoCA

score in Middle Cerebral Artery (MCA) stroke patients was 18.17 ± 5.95 , while in Posterior Cerebral Artery (PCA) stroke patients it was 24.03 ± 4.38 and in Anterior Cerebral Artery (ACA) it was 20.29 ± 5.52 . Vascular territories showed significant ($p < 0.05$) relationship with MoCA scale and non-significant ($p > 0.05$) relationship with Barthel index and Lawton scale. With mild cognitive impairments, ADLs and IADLs were compromised.

Conclusion: MCA stroke patients were more cognitively impaired as compared to ACA and PCA. It was associated with compromised activities of daily living leading to increased functional dependency.

Keywords: Stroke, impairments, cognition, ischemic, hemorrhagic, functional outcome.

INTRODUCTION

Stroke, also known as cerebrovascular accident, is a neurological disorder in which poor blood flow to the brain results in cell death. Stroke patients consist of various symptoms such as sensory disorder, movement defects and cognitive disorder.¹ Stroke is a major cause of morbidity and mortality worldwide.² It is the second leading cause of death and third most leading cause of disability worldwide.³ Stroke is a global disorder which causes both physical and cognitive impairments in patients. Physical impairments include motor and sensory disorders as well as movement disorders while cognitive impairments involve problems in memory, attention, concentration, executive function, language etc. which ranges from mild cognitive impairments (MCI) to severe cognitive impairments.^{4,5}

Cognitive impairment is a common consequence of stroke and one of the major determinants of poor long-term outcomes. Cognitive impairments in the context of stroke or transient ischemic attack (TIA) are a prototype of vascular cognitive impairment.^{6,7} Cognitive impairment ranges from MCI to severe. After stroke, patients have difficulty in remembering, learning new things, focusing, or making decisions that can affect everyday life.

Different cognitive domains like attention and

concentration, memory, executive function, language, visuospatial skills, abstraction, calculation, and orientation are affected, and patients can't continue their routine activities of daily living (ADLs) and instrumental activities of daily living (IADLs). Taken together, cognitive impairment seems to occur most frequently in multiple cognitive domains, typically affecting complex cognitive abilities.⁸ The aim of this study was to investigate the frequency of domain specific mild cognitive impairments and its association with functional outcomes in stroke.

METHODOLOGY

The correlational study was conducted from October 2019 to February 2020. An ethical approval letter (RIPHAH/RCRS/REC/Letter-00646) from the Riphah college of Rehabilitation and Allied Health Sciences was obtained. An informed consent was taken from all participants.

The sample size was calculated through Sample Size Calculator, which was 51 but due to availability of sufficient data, a sample of 300 was taken using non-probability convenience sampling technique.⁹ The research was conducted in government hospital settings and private rehabilitation centers of twin cities, Rawalpindi, and Islamabad. A self-structured

questionnaire was generated with different sections along with the Montreal Cognitive Impairment Assessment Scale (MoCA), Barthel Index (BI), Lawton Instrumental Activities of Daily Living (IADL) Scale.

The MoCA is a 30-point cognitive screening test developed to identify cognitive impairments in stroke patients. A score of 26 or over is normal.^{10,11} The Barthel Index is a reliable scale for disability in stroke patients. The maximal score is 100 (fully functional) and the lowest is 0 (dependent, bedridden).¹² The Lawton Instrumental Activities of Daily Living (IADL) Scale measures a person's ability to perform tasks such as using a telephone, doing laundry, and handling finances. The tool contains eight items, with a score range from 0 (low function) to 8 (high function). Higher score indicates the independent function of patient.^{13,14}

Statistical Analysis: SPSS version 21 was used for data analysis. Bivariate analyses were conducted using the Spearman's correlation for ordinal variables and Pearson correlation for continuous variables, in order to verify various factors. Comparison between the types of vascular territory with MOCA, Lawton scale and Barthel scale was done by running One-way ANOVA test. $p < 0.05$ was considered statistically significant.

RESULTS

The mean age of patients was 57.88 ± 14.1 years with total sample size 300. 241 patients had infarct stroke and 59 suffered from hemorrhagic stroke. 153 patients were right hemiplegic, and 147 patients were left hemiplegic (Table 1). Most commonly involved vascular territory was middle cerebral artery with 237 patients. The correlation of MoCA with other two tools i.e., Barthel index and Lawton scale was calculated in ischemic stroke and hemorrhagic stroke. The correlation of MoCA with Barthel index and Lawton scale with vascular territory MCA, PCA and ACA (Table 2) was calculated where MoCA showed significant relationship with the other scales in MCA.

Mean value of MoCA score in MCA stroke patients was 18.17 ± 5.95 while in PCA stroke patients it was 24.03 ± 4.38 and in ACA stroke patients it was 20.29 ± 5.52 , which means MCA stroke showed more impaired cognition as compared to ACA and PCA type stroke being the least affected. Vascular territories showed significant ($p < 0.05$) relationship with MoCA scale and non-significant ($p > 0.05$) relationship with Barthel index and Lawton scale (Table 3). With mild cognitive impairment, ADLs and IADLs were compromised.

Table 1: Descriptive analysis of Demographics.

Variable	Number %
Male	146(48.7)
Female	154(51.4)
Upper class	25(8.3)
Middle class	203(67.7)
Lower class	72(24.0)
Retired employee	55(18.3)
Teacher	21(7.0)
Housewife	141(47.0)
Labour	39(13.0)
Doctor	4(1.3)
Driver	7(2.3)
Businessmen	33(11.0)
Primary	131(43.7)
Matric	104(34.7)
Intermediate	35(11.7)
Graduation	30(10.0)
Infarct	241(80.3)
Hemorrhage	59(19.7)
MCA	237(79.0)
PCA	32(10.7)
ACA	31(10.3)
Right hemiplegic	153(51.0)
Left hemiplegic	147(49.0)
Duration < 1 year	34(11.3)
1-3 year	186(62.0)
3-6 year	39(13.0)
>6 year	41(13.7)
DM	68(22.7)
HTN	176(58.7)
Smoking	9(3.0)
Cardiac disease	15(5.0)

DISCUSSION

The study showed that cognitive impairments after stroke were quite common in different types of vascular territories. A study of 50 consecutive patients of stroke

Table 2: Correlation of Barthel Index and Lawton scale to MoCA scale in ischemic, hemorrhagic stroke and vascular territories.

Infarct	R value	p value
Barthel index	0.335	0.001
Lawton scale	0.314	0.001
Hemorrhage		
Barthel index	0.185	0.16
Lawton scale	0.053	0.69
MCA		
Barthel index	0.417	0.001
Lawton scale	0.350	0.001
PCA		
Barthel index	0.164	0.369
Lawton scale	-0.093	0.611
ACA		
Barthel index	0.053	0.77
Lawton scale	0.251	0.1

Table 3: Comparison between the types of vascular territory with MOCA, Lawton scale and Barthel scale.

Variable	Vascular Territories	Mean $\pm$ SD	p-value
MoCA	MCA	18.17 $\pm$ 5.95	0.001
	PCA	24.03 $\pm$ 4.38	
	ACA	20.29 $\pm$ 5.52	
Barthel index	MCA	48.83 $\pm$ 21.96	0.071
	PCA	39.50 $\pm$ 19.73	
	ACA	49.58 $\pm$ 23.22	
Lawton scale	MCA	2.46 $\pm$ 4.63	0.706
	PCA	1.90 $\pm$ 1.20	
	ACA	2.06 $\pm$ 0.89	

MoCA: Montreal cognitive assessment scale, **MCA:** Middle cerebral artery, **PCA:** Posterior cerebral artery, **ACA:** Anterior cerebral artery

showed that up to 72% of acute stroke patients had some form of cognitive impairment.¹⁵ We found that 82.6% of the total population was cognitively impaired. The percentage of cognitive impairments in MCA (82.6%) stroke was greater than ACA (74.1%) and PCA (50%).A

study was conducted on 31 patients involving MCA territory, and it was observed that cognitive impairments appeared more frequently when an MCA arterial territory infarction was involved.¹⁶

We routinely encounter many stroke patients with cognitive impairments but the evidence on relationship of cognitive impairments with vascular territory is lacking. Cognitive impairments have a negative effect on recovery and rehabilitation of stroke patients; therefore, they need to be identified early and treated properly. Occlusion in MCA results in stroke with major cognitive dysfunction because frontal lobe is responsible for our memory, decision making, attention and executive functioning. Previous studies showed no correlation between vascular territory and cognitive impairments.¹⁷

This correlational study showed that post stroke cognitive impairment is frequent with MCI occurring more in MCA stroke as the mean value of MoCA score was 18.17 $\pm$ 5.95 out of 30 indicating impaired cognition. The mean value of MoCA scale for PCA and ACA stroke were higher, which shows there was some degree of cognitive impairment. The relationship of vascular territories with MoCA scale was significant ($p < 0.05$), which means different severity of cognitive impairments. Visuospatial/executive functioning and memory was impaired in more than half of the patients found with cognitive impairment. These domains have a direct impact on functional recovery, rehabilitation, and the quality of life of stroke patients.

MCA stroke subjects have more impaired cognition than PCA and ACA. The relationship of MCA stroke with the outcome measures was calculated, which was found significant ($p = 0.001$) and mild positive ($r = 0.417$ for Barthel index, $r = 0.345$ for Lawton scale). The non-significant relationship of PCA stroke with Barthel ($r = 0.164$, $p = 0.369$) and Lawton scale ($r = -0.093$, $p = 0.611$) was found and similarly the relationship of ACA stroke with Barthel ($r = 0.053$, $p = 0.775$) and Lawton scale ($r = 0.251$, $p = 0.172$) was also insignificant, which means MCA stroke results in more functional disability in ADLs and IADLs than PCA and ACA strokes. A study concluded that MCA stroke has greater arm and leg involvement making them poor candidates for rehabilitation.¹⁸

The relationship of Barthel index of ADLs and Lawton scale of IADLs with vascular territory showed non-significant relationship ($p = 0.071$ and $p = 0.706$, respectively), which indicates problems in performing ADL and IADL has no obvious link with affected vascular territory. A study from Finland reported that 83% of stroke subjects showed cognitive impairment which was associated with functional dependence at 15

months.¹⁹

Few limitations need to be considered here. Data were collected from only those patients who were able to communicate and was not collected of all three vascular territories because of which comparison was inefficient. The study focused only on MCI. Further studies are necessary to determine the importance of cognitive dysfunction, as it is commonly neglected. Findings of study are limited to the cases of stroke in the hospital setting, future studies should attempt to evaluate the cases which are exclusively treated in communities.

CONCLUSION

There was an association of domain specific cognitive impairment with functional outcomes in stroke patients. MCA stroke patients were more cognitively impaired as compared to ACA and PCA. It was associated with compromised activities of daily living.

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REFERENCES

1. Einstad MS, Saltvedt I, Lydersen S, Ursin MH, Munthe-Kaas R, Ihle-Hansen H, et al. Associations between post-stroke motor and cognitive function: a cross-sectional study. *BMC Geriatrics* 2021;21:1-0.
2. Johnson W, Onuma O, Owolabi M, Sachdev S. Stroke: a global response is needed. *Bull World Health Organ* 2016;94:634.
3. Chung CP. Types of stroke and their differential diagnosis. *Primer on Cerebrovascular Academic Press. Diseases* 2017;372-6.
4. Kalara RN, Akinyemi R, Ihara M. Stroke injury, cognitive impairment and vascular dementia. *Biochimica et Biophysica Acta (BBA)-Molecular Basis Dis* 2016;1862:915-25.
5. Paker N, Buğdaycı D, Tekdöş D, Kaya B, Dere Ç. Impact of cognitive impairment on functional outcome in stroke. *Stroke Res Treatment. Volume 2010 | Article ID 652612 | https://doi.org/10.4061/2010/652612*
6. Lin M, Ren J, Wu J, Huang J, Tao J, Chen L, Liu Z. The Prognostic Value of Domain-Specific Cognitive Abilities Assessed by Chinese Version of Oxford Cognitive Screen on Determining ADLs Recovery in Patients with Post-Stroke Cognitive Impairment. *Evidence-Based Compl Altern Med Volume 2022 | Article ID 1084901 | https://doi.org/10.1155/2022/1084901*
7. Liu W, Wong A, Au L, Yang J, Wang Z, Leung EY, et al. Influence of amyloid- β on cognitive decline after stroke/transient ischemic attack: three-year longitudinal study. *Stroke*. 2015;46:3074-80.
8. Jokinen H, Melkas S, Ylikoski R, Pohjasvaara T, Kaste M, Erkinjuntti T, et al. Post-stroke cognitive impairment is common even after successful clinical recovery. *Eur J Neurol* 2015;22:1288-94.
9. Montreal Cognitive Assessment (MoCA) Test: Scoring & Accuracy". Very well. Retrieved 12 June 2017.
10. Yang Y, Fuh J, Mok VC. Vascular contribution to cognition in stroke and Alzheimer's disease. *Br Sci Adv* 2018;4:39-48.
11. Nakling AE, Aarsland D, Næss H, Wollschlaeger D, Fladby T, Hofstad H, et al. Cognitive deficits in chronic stroke patients: neuropsychological assessment, depression, and self-reports. *Dementia Geriatric Cognitive Disord Extr* 2017;7:283-96.
12. Robert Teasell MD, Hussein N. Clinical consequences of stroke. *Evidence-Based Review of Stroke Rehabilitation. Can Stroke Net* 2016:1-30.
13. Arauz A, Rodríguez-Agudelo Y, Sosa AL, Chávez M, Paz F, González M. Vascular cognitive disorders and depression after first-ever stroke: the Fogarty-Mexico Stroke Cohort. *Cerebr Dis* 2014;38:284-9.
14. Jokinen H, Melkas S, Ylikoski R, Pohjasvaara T, Kaste M, Erkinjuntti T, et al. Post-stroke cognitive impairment is common even after successful clinical recovery. *Eur J Neurol* 2015;22:1288-94.
15. Zheng F, Yan L, Zhong B, Yang Z, Xie W. Progression of cognitive decline before and after incident stroke. *Neurology* 2019;93:e20-8.
16. Zietemann V, Georgakis MK, Dondaine T, Müller C, Mendyk AM, Kopczak A, et al. Early MoCA predicts long-term cognitive and functional outcome and mortality after stroke. *Neurology* 2018;91:e1838-50.
17. Saa JP, Tse T, Baum C, Cumming T, Josman N, Rose M, et al. Longitudinal evaluation of cognition after stroke—A systematic scoping review. *PloS one* 2019;14:e0221735.
18. Nijse B, Spikman JM, Visser-Meily JM, de Kort PL, van Heugten CM. Social cognition impairments in the long term post stroke. *Arch Physical Med Rehabil* 2019;100:1300-7.
19. Lingo Van Gilder J, Hooyman A, Peterson DS, Schaefer SY. Post-stroke cognitive impairments and responsiveness to motor rehabilitation: a review. *Curr Phys Med Rehab Rep* 2020;8:461-8.
20. Turunen KE, Laari SP, Kauranen TV, Uimonen J, Mustanoja S, Tatlisumak T, Poutiainen E. Domain-specific cognitive recovery after first-ever stroke: a 2-year follow-up. *J Int Neuropsychol Soc* 2018;24:117-27.

Geriatric ear diseases; A teaching hospital experience in Sargodha, Pakistan

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Objective: To highlight the pattern of ear diseases among the elderly to provide an objective basis to plan cost effective healthcare for the geriatric population in Pakistan.

Methodology: This retrospective study was done in the Department of Otorhinolaryngology, Niazi Welfare Foundation Teaching Hospital, Sargodha from January 2022 to December 2023. Sample of 644 patients, ≥ 60 years, who presented with ear diseases, were enrolled. They were categorized into four groups based on age. The history, comprehensive clinical examination findings and the record of relevant investigations were evaluated and definitive diagnosis was confirmed. The SPSS version 23 was used for statistical analysis.

Results: Study comprised majority (61.6%) males.

The predominant age group was 60-69 years and senile hearing loss was found to be the highly prevalent (29.2%) disease among all age groups, followed by impacted cerumen (24.4%) and chronic suppurative otitis media (17.7%).

Conclusion: The highest number of cases belonged to the age group 60-69 years and senile hearing loss was highly prevalent. Primary care physicians should be trained to do otoscopic examination, as an essential component of basic assessment of elderly patients, for the timely referral to specialist clinics, thus improvise the chances of better care of aged ears.

Keywords: Geriatric, otitis externa, otitis media, presbycusis.

INTRODUCTION

Aging is a natural process. Worldwide rate of the geriatric population is reaching up to 690 million, whereas in Pakistan, it touches the figure of 11.3 million; further, an upsurge is expected to 43.3 million by 2050.¹ WHO has set the goal of the decade (2021-2030) as: “the process of developing and maintaining the functional ability that enable well-being in older age”.² The human body is made up of cells, and the course of aging affects the infrastructure of this cellular system at all levels.³ The aged ear is unique in its altered anatomy and declined functionality; which is exhibited up to a variable extent among different individuals.⁴ The changes in the elasticity of the skin and the cartilage of the external ear lead to its collapse; whereas the tympanic membrane and ossicles stiffen, however, the degenerating cochlea leads to higher frequency hearing loss.⁴ All these changes are permanent and progressive to a variable extent, so in this detrimental period of life, late diagnosis renders an individual prone to many difficulties, including impaired cognition as well.⁵ Most common cause for elderly population presenting in otolaryngology clinics is due to problems related to the ear (24.2%) followed by balance disorders (15.3%).⁶ The life expectancy for both genders, in Pakistan, has

reached 65.9 (63.8–67.8) years.⁷ Geriatric ear diseases are under looked in our society. This study aimed to understand the pattern of ear diseases among the elderly population in Pakistan, so healthcare providers can plan cost-effective programs to control and prevent such diseases.

METHODOLOGY

This retrospective study was conducted at the Department of Otorhinolaryngology of Niazi Welfare Foundation Teaching Hospital, Sargodha. The data of the patients visited from 1st January 2022 to 31st December 2023 was included in the study. Ethical approval was obtained from IRB (Ref No. NMDC/PMC/035/24). The process of data collection and analysis was done for one month.

Records of all the patients aged ≥ 60 years (the retirement age for most public workers in Pakistan), who presented with ear diseases were included in the study, regardless of their gender and race. Demographic data like age, gender, occupation and residential area, history and physical examination findings and the reports of relevant investigations including audiological assessment and laboratory results like basic blood tests, aural swab tests for culture and sensitivity etc. were studied thoroughly to

confirm the accuracy of diagnosis. The exclusion criteria were incomplete records. The patients were divided in four groups, based on their age; Group A (60-69 years), Group B (70-79 years), Group C (80-89 years) and Group D (≥ 90 years).

Statistical Analysis: The SPSS version 23 was used for data analysis. The frequency was calculated for quantitative data like age groups. A statistically significant $p < 0.001$ was calculated via paired samples T-test.

RESULTS

Out of 644 patients, 397 (61.6%) were males and 247 (38.4%) females (Fig.). The percentages of the participants were 59.3% in group 'A' (60-69 years), 24.1% in group 'B' (70-79 years), 14.6% in group 'C' (80-89 years) and 2% in group 'D' (≥ 90 years).

Senile hearing loss (SHL) was found as the most prevalent (28.9%) disease among all participants. Other

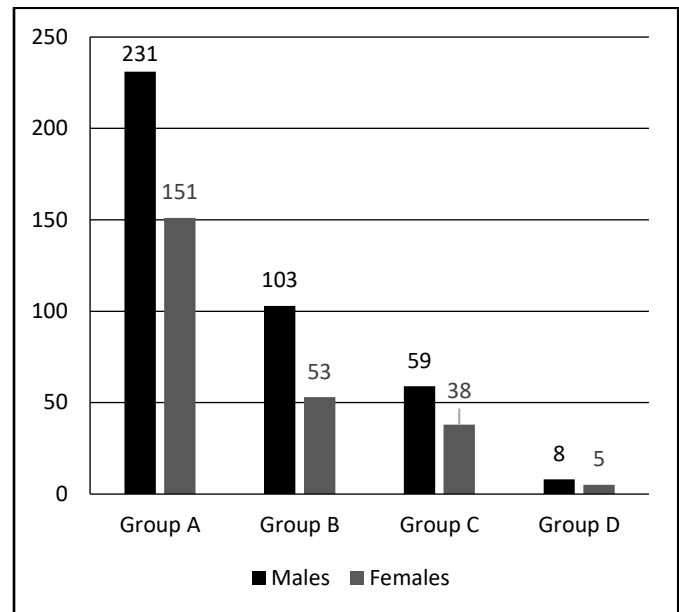


Fig. 1: Gender distribution (n=644).

Table 1: Frequency of diseases among different age groups.

Group A (60-69 years)	Group B (70-79 years)	Group C (80-89 years)	Group D (≥ 90 years)
SHL (26.4%) Wax (22.5%) CSOM* (19.4%) OE ¹ (12.8%) OMY ² (8.1%) Vertigo (2.1%) OMY+OE (1.6%) Referred Otalgia (1.6%) Tinnitus (1%) ASOM ³ (1%) Eustachian Catarrhal (1%) Functional (0.5%) Pruritus (0.5%) Boil (0.3%) External ear trauma (0.3%) M.O.E ⁴ (0.3%) Myringitis (0.3%) Pinna growth (0.3%)	SHL (34.6%) Wax (24.4%) CSOM (16.7%) OE (9.6%) OMY (4.5%) ASOM (1.9%) Functional (1.9%) OMY+OE (1.9%) Vertigo (1.9%) BPPV (0.6%) Eustachian Catarrhal (0.6%) Labyrinthitis (0.6%) Tinnitus (0.6%)	Wax (33.3%) SHL (29%) OE (12.9%) CSOM (11.8%) OMY (7.5%) Tinnitus (2.2%) Eustachian Catarrhal (1.1%) OMY+OE (1.1%) Vertigo (1.1%)	SHL (30.8%) CSOM (23.1%) Wax (15.4%) Boil (7.7%) OE (7.7%) OMY (7.7%) Vertigo (7.7%)
N=382	N=156	N=93	N=13

*Chronic suppurative otitis media, 1 Otitis Externa, 2 Otomycosis, 3 Acute suppurative otitis media, 4 Malignant otitis externa.

commonly seen conditions in the total study population were 24.4% impacted cerumen, 17.7% chronic suppurative otitis media (CSOM), 12% otitis externa (O.E) and 7.1% otomycosis (OMY) followed by few miscellaneous conditions in smaller percentages (Table 1).

DISCUSSION

In this study, the most commonly presented age group was 'A' (60-69 years). In the early period of old age, majority of the subjects are independent and mobile hence they may access the healthcare facilities earlier. The male gender was found dominant in all age groups,

this trend is already seen in other studies,⁸ and it might be representing our society's trend about financial dependency of women and ignorance about their health. The senile hearing loss (28.9%) is proved as the highly prevalent ontological disease of elderly. According to WHO, globally one third of the people aged ≥ 65 years are suffering from hearing impairment, and in 2025, this ratio is expected to rise to 1.2 billion at ≥ 60 years of age.⁹ Marius et al found the mean age for early onset of senile hearing loss as 59.48 ± 9.80 years, with a male-to-female ratio of 1.23.¹⁰ Faisal et al, found the prevalence of presbycusis in the age group of 60-69 years as 65.2%.¹¹ The reduced ability to understand sounds negatively affects the cognition and psychosocial abilities of an elderly person and may cause social isolation.¹² Impacted cerumen (wax) was the second most common presenting cause seen in the groups A (60-69 years) and B (70-79 years), and the leading cause of presentation in group C (80-89 years). Topus had almost similar result in his study.¹³ The increased stiffness of the vibrissae presents in the auditory canal and the structural changes in the canal's cartilage, promote the impaction of cerumen in the elderly. This condition leads to several other complications, like decreased hearing and itching in the ear which provoke a desire to scratch frequently, eventually it may traumatize the canal skin and lead to the otitis externa.¹⁴ If the tympanic membrane perforates due to self-instrumentation or any other cause, it may progress to otitis media at this late stage of life. Depression and impaired cognition in the elderly population improve after aural toilet.¹⁵ The stiffened tympanic membrane, atrophied tensor veli muscle, calcification in the ossicular joints and the eustachian tube augment the difficulty in hearing for a hearing compromised aged person.¹⁶

Among the infective diseases, group A, B and D showed the top rate of CSOM followed by O.E and OMY; in Group C the rate of O.E was slightly higher than the CSOM. Sriprakash also had similar results, CSOM (14.4%) followed by the O.E and OMY.¹⁷ Factors associated with the pathogenesis of CSOM are poor socioeconomic status and lack of hygiene; though it mostly starts in childhood or early adulthood, the custom of home remedies, lack of awareness about ear care and inaccessibility to prompt healthcare facilities due to financial strains lead to the persistence of disease.¹⁸

The OMY may represent a low immunity in the elderly. The hot and humid environment, habit of self-instrumentation in the ear, instillation of mustard oil etc. promote the growth of pathogenic fungi in the ears.¹⁹ The other miscellaneous infectious diseases were scarcely seen, and were mostly affecting the group A (60-69 years).

The group D, nonagenarian subjects (≥ 90 years of age), were the least common visitors. The life expectancy is low in Pakistan; moreover, financial strains, decreased mobility, and transportation difficulties halt the access of this population to the healthcare providers.

The impacted cerumen, fungal debris, swollen ear canals, perforated ear drums, and congested middle ear mucosa further deteriorate the ability to hear in a hearing-compromised aged ear. The prolonged effects of reduced hearing leads to speech problems and cognitive dysfunction in elderly population, as the neurocognitive mechanism is deprived of auditory stimulation.

More data are required from different regions of the country on this topic, also the prospective studies should be done for identification of possible risk factors involved in the pathogenesis of these diseases, for a timely diagnosis and to provide a basis for healthcare providers to plan the preventive strategies. The pathophysiological changes are needed to study to recognize the structural changes. The basic ear examination ought to be a part of the geriatrics' general assessment. Primary care physicians and interns should be trained to effectively filter the patients for an early referral to the specialist clinic. Moreover, healthcare facilities should be accessible and economical for all social classes.

CONCLUSION

Presbycusis followed by impacted cerumen and CSOM are the most prevailing diseases among the geriatric population. The early steps should be taken to detect the possible pathogenic factors; to institute proper treatment and the rehabilitative services according to the need of an individual, to make old age tolerable for the geriatric population, and to keep them functional at all possible levels.

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REFERENCES

1. Geriatric Care in Pakistan: Current Realities and Way Forward. PJP 2022;11:214-219.
2. WHO. Decade of healthy ageing: baseline report. World

- Health Organization; 2021 Jan 14.
3. Chalise HN. Aging: basic concept. *Am J Biomed Sci Res* 2019;1:8-10.
4. Alberti PW. The anatomy and physiology of the ear and hearing. *Occupational exposure to noise: Evaluation prevention, and control.* 2001:53-62.
5. Brotto D, Benvegnù F, Colombo A, de Filippis C, Martini A, Favaretto N. Age-related changes in auditory perception. *Hearing loss in the elderly: aging ear or aging brain? Aging Clin Exp Res* 2023;35(11):2349-54.
6. Özler GS, Yengil E. Why do geriatric patients visit otorhinolaryngology? *Ear Nose Throat J* 2016;95:224-9.
7. Azam M, Uddin I, Saqib N. The determinants of life expectancy and environmental degradation in Pakistan: evidence from ARDL bounds test approach. *ESPR* 2023;30:2233-46.
8. Sahoo SR, Sarma M. Otological disorders in geriatric population: A study. *Indian J Gerontol* 2021;35:8-16.
9. Wang J, Puel JL. Presbycusis: an update on cochlear mechanisms and therapies. *J Clin Med* 2020;9:218-22.
10. Flatin MC, do Santos Zounon AA, Ametonou CB, Bouraima FA, Kimba R, Adjibabi W, et al. Impact and Factors Associated with Presbycusis among 50 Years Old People of Parakou and Over in 2021. *Int J Otorhinolaryngol Head Neck Surg* 2021;11:56-73.
11. Rafiq F, Ali MM, Afridi A. Frequency of Age-related Hearing Loss in General Population of 60 Years and above. *PJMHS* 2020;14:508-10
12. Seo J. Association between age-related hearing loss and cognitive decline. *J Korean Med Assoc* 2023;66:568-71.
13. Topuz MF. Assessment of diagnosis and treatment of geriatric patients in otorhinolaryngology. *J Surg Med* 2020;4:496-500.
14. Sadiq SM, Nagra SR, Ahmed SA, Ahmed M, Khalil M, Ali Z. Cerumen Impaction: Its Associated Risk Factors and Clinical Presentation. In *Med. Forum.* 2022;33(9).
15. Schwartz SR, Magit AE, Rosenfeld RM, Ballachanda BB, Hackell JM, Krouse HJ, et al. Clinical practice guideline (update): earwax (cerumen impaction). *Otolaryngol Head Neck Surg* 2017;156:S1-29.
16. Önerci TM, Altunay ZÖ. *Diagnosis in Otorhinolaryngology: An Illustrated Guide.* Springer Nature; 2021.
17. Sriprakash V. Ear complaints in elderly patients attending ENT OPD. *J Res Otorhinolaryngol Head Neck Surg* 2015;1:17-20.
18. Dayasena RP, Dayasiri MB, Jayasuriya C, Perera DS. Aetiological agents in chronic suppurative otitis media in Sri Lanka. *Aust J Med* 2011;4:101-5.
19. Abdullah I, Alzaid SA, Aljasser MF, Khwaji MO, Ibrahim AB, Bukhamseen N, et al. Literature Review on Patient Demographics, Risk Factors and Causative Agents of Otomycosis. *IJPRAS* 2019;8(4-2019):111-5.
20. Völter C, Götze L, Dazert S, Wirth R, Thomas JP. Impact of hearing loss on geriatric assessment. *Clin Interv Aging* 2020;15:2453-67.

Prevalence of trochanteric bursitis in patients with grade-I & grade-II knees osteoarthritis

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Objective: To determine the prevalence of trochanteric bursitis in patients with grade-I and grade-II knee osteoarthritis (OA).

Methodology: This cross-sectional survey employed non-probability convenient sampling, enrolling 384 patients aged 40 to 60 years with grade I and grade II knee OA and consistent symptoms of lateral hip pain. Both genders were selected from the Department of Orthopedic & Physiotherapy of Combined Military Hospital Lahore, Mayo Hospital Lahore, and Jinnah Hospital Lahore. Pain and knee OA were assessed using the WOMAC scale, while prevalence of trochanteric bursitis was measured using the Lower Extremity

Functional Scale (LEFS). Data analysis was done using SPSS 26.

Results: Mean age of the 384 patients was 46.43±5.662 years. Based on the WOMAC questionnaire, 33.3% patients reported knee pain, 50% showed stiffness, and 25% had trouble in walking, performing daily living activities. Prevalence of trochanteric bursitis was 36.1% using LEFS.

Conclusion: A considerable proportion of knee OA patients may experience additional pain and functional limitations due to the coexistence of trochanteric bursitis.

Keywords: Bursitis, knee osteoarthritis, patients.

INTRODUCTION

Osteoarthritis (OA) is a common degenerative joint disorder characterized by the progressive breakdown of articular cartilage, leading to pain, stiffness, and loss of function.¹ While the primary focus of OA research has often been on the knee joint itself, recent studies have highlighted the significance of extra-articular structures in contributing to the overall symptomatology of OA.² Trochanteric bursitis, an inflammation of the bursa located over the greater trochanter of the femur, is one such extra-articular condition that has gained attention due to its potential association with knee OA.³

The knee joint is a complex structure consisting of various components.⁴ Recent research has expanded our understanding to include the role of adjacent soft tissues and structures in influencing the clinical presentation of knee OA.⁵ Trochanteric bursitis, typically associated with hip pain, has been found to potentially contribute to the overall discomfort experienced by knee OA patients.⁶ Understanding the potential association between trochanteric bursitis and knee OA severity holds clinical relevance.⁷ Accurate diagnosis and targeted treatment are essential for effectively managing OA.⁸

Arel et al, reported that trochanteric bursitis was connected to gender; more than 70% of greater trochanteric pain syndrome (GTPS) patients were females.⁹ Axelrod et al, concluded that the choice of surgical procedure might not influence the incidence of

trochanteric pain.¹⁰ Berney et al, stated that, given the 8.5% incidence, explicit pre-operative counseling on trochanteric bursitis should be done prior to total hip arthroplasty.^{11,12} This study aimed to determine the prevalence of trochanteric bursitis in patients with grade-I and grade-II OA.

METHODOLOGY

This cross-sectional survey employed non-probability convenient sampling and enrolled 384 patients from Departments of Orthopedic & Physiotherapy of Combined Military Hospital Lahore, Mayo Hospital Lahore, and Jinnah Hospital Lahore and was conducted from March to August 2023. It was approved by research ethics commission (Ref No. HU/FAHS/ECRB/23/33).

With 95% CI and 5% margin of error the sample size was calculated from Qualtrics software. Patients aged 40 to 60 years of both gender with grade-I and II knee OA and consistent symptoms of lateral hip pain were included in the study. The exclusion criteria encompass individuals with acute pain, inflammation, recent fractures, red flag signs post-knee trauma, prolonged immobilization, pregnancy, or a history of arthroplasty, rendering them unsuitable for participation or treatment.

Pain and knee OA were assessed using Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scale.¹³ The WOMAC sub scales demonstrated high internal consistency (Cronbach's

alpha: pain = 0.91, stiffness = 0.81, physical function = 0.84) and satisfactory test-retest reliability (ICCs: pain = 0.86, stiffness = 0.68, physical function = 0.89), indicating its reliability. Trochanteric bursitis was measured using the LEFS.¹⁴ The LEFS Greek questionnaire is employed to assess the functional capacity of elderly individuals living in the community. Strong reliability, akin to both the original version and its Italian adaptation. This suggests that the LEFS-Greek could serve as a dependable instrument for evaluating functionality among individuals with lower extremity musculoskeletal issues.

Statistical Analysis: Data were analyzed using SPSS version 26.

RESULTS

Mean age of the participants was 46.43 ± 5.662 years. The patients had knee OA grades - I and II, representing mild to moderate stages of the disease. The results showed that 33.3% of the patients had knee pain, which was the most common response. Additionally, 50% of the patients reported stiffness in their knees, and 25% reported difficulty in walking and performing activities of daily living (ADLs). LEFS showed that 36.1% of the patients had trochanteric bursitis (Table 1).

Table 1: Frequencies of LEFS response.

LEFS Response	Frequency	%
0 TO 20 responded None	0	0
21 TO 40 responded Slight	207	53.9
41 TO 60 responded Moderate	157	40.9
61 TO 80 responded Severe	20	5.2
Total	384	100.0

LEFS= Lower Extremity Functional Scale

Table 2: Frequencies of WOMAC Stiffness Scale Response.

Response	Frequency	%
0 to 4 responded No	148	38.5
5 to 8 responded YES	236	61.5
Total (n)	384	100.0

Frequencies of WOMAC Stiffness Scale Response are shown in Table 2. Table 3 shows frequencies of WOMAC Difficulty Scale Response.

Table 3: Frequencies of WOMAC Difficulty Scale Response.

Response	Frequency	%
0 to 17 responded None	32	8.3
18 to 34 responded Slight	152	39.6
35 to 51 responded Moderate	159	41.4
52 to 64 responded Severely	41	10.7
Total (n)	384	100.0

DISCUSSION

Our study's identification of a substantial prevalence of trochanteric bursitis underscores the importance of considering these associations in clinical practice. The findings of our study resonate with the work of Weng and Chen, who emphasized the potential impact of trochanteric bursitis on knee OA patients' functional limitations and quality of life.⁷ They stated that trochanteric bursitis could contribute to hip pain and mobility impairments, further highlighting the interconnectedness of adjacent structures and their influence on knee OA symptomatology.⁷

The coexistence of trochanteric bursitis with knee OA may extend beyond symptomatology to encompass the influence of comorbidities on disease progression. A study by Muraki et al, proposed that their co-occurrence could lead to heightened pain sensitivity and reduced physical activity.¹⁵ Our study's identification of trochanteric bursitis in knee OA patients substantiates the notion that concurrent pathologies can contribute to a more complex clinical picture.

To contextualize and validate the study's findings, it is crucial to compare them with relevant previous articles. Smith et al, conducted a similar investigation on a population of knee OA patients with a mean age like the present study. They reported a higher prevalence of trochanteric bursitis (4.8%) among knee OA grade-I and II patients.¹⁶ The difference in prevalence between the two studies may be attributed to variations in sample size, geographic location, or diagnostic criteria used to identify trochanteric bursitis. In another study by Jones et al, reported prevalence of trochanteric bursitis in their study was 1.9%, which is slightly lower than the present study's findings.¹⁷

The variation in prevalence might be explained by differences in knee OA grading. This study highlights the examination of the early stages of knee OA, which can help control the significant symptoms of trochanteric bursitis and set awareness goals.

Cross-sectional design lacks causality and temporal sequencing determination for trochanteric bursitis

prevalence. The lack of a control group hinders the comparison of knee OA prevalence. Trochanteric bursitis prevalence based on subjective self-reporting. The study may not account for confounding factors affecting trochanteric bursitis prevalence.

CONCLUSION

A considerable proportion of knee OA patients may experience additional pain and functional limitations due to the coexistence of trochanteric bursitis.

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REFERENCES

1. Berenbaum F. Osteoarthritis is an inflammatory disease (osteoarthritis is not osteoarthrosis!). *Osteoarth Cartil* 2013;21:16-21.
2. Neogi T. The epidemiology and impact of pain in osteoarthritis. *Osteoarthritis Cartilage*. 2013;21:1145-53.
3. Chhabra A ST, Carrino JA, Aman ZS. Trochanteric Bursitis Revisited: An Overview of Etiology, Diagnosis, and Management. *Curr Rev Musculoskelet Med* 2020;13:338-47.
4. Abulhasan JF, Grey MJ. Anatomy and physiology of knee stability. *J Func Morphol Kinesiol* 2017;2:34.
5. Lespasio MJ, Piuze NS, Husni ME, Muschler GF, Guarino AJ, Mont MA. Knee osteoarthritis: a primer. *Perm J* 2017;21:16-183.
6. Dzidzishvili L, Parrón Cambero R, Mahillo Fernández I, Llanos Jiménez L. Prognostic factors of trochanteric bursitis in surgical-staged patients: a prospective study. *Hip Int* 2022;32:530-6.
7. Weng MC LC, Chen CH. Association between trochanteric bursitis, osteoarthritis, and total hip replacement surgery: a case-control study. *Arthr Res Ther* 2018;20:7.
8. Ghouri A, Conaghan PG. Prospects for therapies in osteoarthritis. *Calcif Tissue Int* 2021;109:339-50.
9. Aref SF, Al-Rawi ZS, Jalal AM. Joint Mobility among Patients with Trochanteric Bursitis in Erbil-Iraq. *Indian J Public Health Res Deve* 2023;14:302-8.
10. Axelrod D, Madden K, Khan H, Banfield L, Winemaker M, DeBeer J, et al. Trochanteric pain, and total hip arthroplasty: a systematic review of the literature. *Curr Orthop Pract* 2020;31:400-7.
11. Berney M, Bowe A, Quinn M, Quinlan J. A painful problem: trochanteric bursitis following total hip arthroplasty. *Acta Orthop Belg* 2020;86:e Suppl 3:21-4.
12. Lange J, Tvedesøe C, Lund B, Bohn MB. Low prevalence of trochanteric bursitis in patients with refractory lateral hip pain. *Dan Med J* 2022;69:A09210714.
13. Riddle DL, Perera RA. The WOMAC Pain Scale and crosstalk from co-occurring pain sites in people with knee pain: A causal modeling study. *Phys Ther* 2020;100:1872-81.
14. Mehta SP, Fulton A, Quach C, Thistle M, Toledo C, Evans NA. Measurement properties of the lower extremity functional scale: a systematic review. *J Orthop Sports Phys Ther* 2016;46:200-16.
15. Muraki S AT, Oka H. Trochanteric bursitis is prevalent and associated with worse pain and function: the Ko - Gane Study. *J Orthop Sci* 2014;19:933-8.
16. Smith J HW, Carbone W. Increased prevalence of trochanteric bursitis in hip osteoarthritis. *Clin Orthop Relat Res* 2013;471:3212-8.
17. Jones A RM, Ledingham J. Importance of low-grade inflammation in osteoarthritis. *Osteoarth Cartil* 1997;5:76-78.

Predictors of perception of young physician about their career: A cross-sectional study

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Objective: To assess the mentality and clarity of junior doctors and medical students regarding their career.

Methodology: This cross-sectional study was conducted at Fauji Foundation hospital, Rawalpindi. For duration of one month. The sample size of the study was 350. Non-probability convenience sampling method was used to collect data. All medical students and junior doctors were included in the study. A self-made questionnaire based on previous studies was used in the study.

Results: Mean age of participants was 22.56 years. Most were medical students (64%) and remainders were house officers. A majority (53.1%) expressed clarity

regarding their future and career pathway while 45.4% were uncertain about their future. Career counselling was significantly associated with improved clarity regarding the future. The percentage of young doctors planning on going abroad was 41.7%, while 25.7% of the young doctors planned on staying in Pakistan.

Conclusion: The medical education system in Pakistan has shown a trend of increasing desire of the young doctor to move abroad. This causes a shortage of doctors in the country. Career counselling was shown to impact decision making capacity of the young doctor.

Keywords: Medical education, doctors, career choice, predictors, perception.

INTRODUCTION

The motivation behind choosing medicine as their career and their choices during their initial years shape an aspiring doctor's life. The steps and decision taken during this time have a lasting impact on their future. Their decision has implications that can be felt at a national and international level. The decision to seek employment abroad is something that has an impact at a national level. The brain drains of aspiring doctors have caused a shortfall of doctors in developing countries.

There are multiple reasons for moving abroad. One such factor is income, which is a significant factor that can impact a person's decision to stay in their home country or go abroad. A study from Malawi found that young doctors were willing to stay in Malawi if their salary was increased.¹ Mandeville et al reported that those who had done "A" and "O" levels were more likely to leave their home country.²

Covid pandemic of 2020 has significantly impacted the medical student's mentality. A study from Japan found that there was a decreasing trend among medical students who expressed a desire to move abroad.³ Career pathways available to young doctors are numerous; thanks to the advances that health sciences have made and increase in international travel. Those with a clear role model in the family tend to be clearer minded.⁴

Gender has been shown to play a significant role in career pathways.⁵⁻⁷ Females tended to show specialties that leaned towards primary care and males tended to lean towards working in public sector as compared to females. This study aims to investigate the various factors that impact young doctors and medical students' career decisions.

METHODOLOGY

This cross-sectional study was carried out at Fauji Foundation Hospital, Rawalpindi for duration of one month in 2023. The study was approved by IRB of Fauji Foundation Hospital (No. FF/FUMC/215-317/Phy/23) and an informed consent was taken from all participants. The sample size was 350. It was calculated using the WHO calculator keeping confidence levels at 95%, non-probability convenience sampling method was used to collect the data.

All medical students and junior doctors were included in the study. Medical students who had joined MBBS <6 months and doctors who have completed their specialist training were excluded from the study. A self-made questionnaire based on previous studies was used in the study. The questionnaire was initially tested on a small group of 30 people. It was tested for clarity of questions and ease of understanding.

The interviewer read out the questions and entered the participant's response. The interviewers were instructed to only ask the question word for word without any personal input or insight of the question. The google forms was used due to its ease of use in entering data and basic analysis. the data was then imported into SPSS for further analysis.

Statistical Analysis: The data were analyzed using both google forms and SPSS version 22.

RESULTS

The mean age of the participant was 22.56 years. Females constituted 73.1% of the participants. The participants included 36% of house officers. 9.4% first year students, 11.4 % second year students. 11.4 % third year students, 16.6% fourth year students and 15.1% final year students. The majority belonged to urban areas (88.3%) and were unmarried (89.4%). The number of participants that had done A levels was 15.1%.and the rest had done FSE intermediate.

Most participants (52.6%) had family members who were already in the medical field. A significant majority (61.1%) got guidance from a close friend or family

member. A significant portion wanted to pursue medicine since childhood (35.1%), while some decided to pursue medicine during their matric (26.9%) or FCSE intermediate year (23.7%). The reasons for joining medical field ranged from wanting to help others (33.1%), PayScale of doctors (4.0), perceived social status of medicine (3.4%), influence from family and friends (16.6%), were forced upon by parents (7.1%), lack of other career paths (15.4%), opportunity for research and challenge (13.1%), interest in field (0.6%) and personal satisfaction (0.9%). A vast majority (82.9%) had been inspired by a doctor or professor during their medicine school year or house job. Participants scoring is shown in the Table 1.

A majority (53.1%) expressed clarity regarding their future and career pathway while 45.4% were uncertain about their future. Those that wanted to work in the government sector were 27.7% while 21.1% wanted to work in private sector and 48.9 % were undecided. Career counselling was heard by 93.7% of the young doctors but only 22.3% had taken career counselling. Even though most (93.7%) considered career counselling to be essential. Career counselling was significantly associated

Table 1: Participants scoring.

Year	With Research Publications	Have Attended Conference	Plan to Go Abroad	Clear About Their Future	Work in Government Sector	satisfied with Decision to Become Doctors
First year	0%	27%	36%	55%	36%	90%
Second year	10%	55%	35%	55%	25%	80%
Third year	0%	47.5%	15%	45%	35%	83%
Fourth year	10%	38%	52%	55%	17%	76%
Final year	26%	91%	40%	45%	28%	94%
House officer	24%	83%	50%	57%	29%	83%

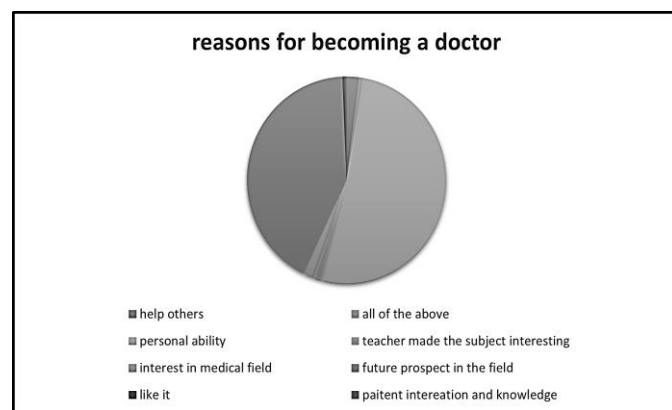


Fig. 1: Reasons for profession.

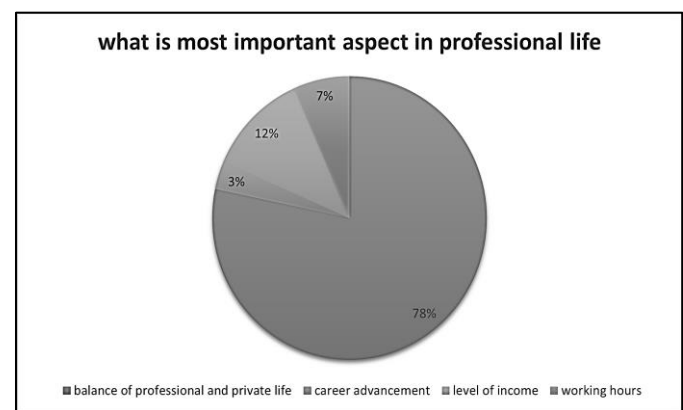


Fig. 2: Important aspect in professional life.

with improved clarity regarding the future ($p=0.010$). The percentage of doctors that was satisfied with their decision to become doctors was 84%. The impact of their career and studies was believed to impact their personal life by 84% of the young doctors. Reasons for becoming doctor are shown in Fig. 1. Most important aspect in professional life is shown in Fig. 2.

DISCUSSION

Our study found that only 4.3% of were interested in basic sciences. The majority showed more interest in clinical subjects. A study conducted in Netherlands found that students preferred clinical oriented studies.⁸ Medical students worldwide prefer clinical career as compared to teaching career. Onakpoya et al, did a study on medical students and found that only 6.2% of the participants were considering a career in anatomy.⁹

A multi-center study from Pakistan found that 7.9 % of the medical students in Dow International Medical College and Jinnah Medical and Dental College were interested in going to basic sciences and non-clinical specialty.¹⁰ Basic sciences form the building block of medical knowledge. The lack of motivated teachers will result in medical students with shallow medical knowledge.

The post covid era has brought along with-it new challenges. Studies have shown that more medical students are preferring to move aboard instead of staying in their native countries.¹¹ A study from Japan reported that 68% of the medical student in Japan showed a desire to move aboard.¹²

Our study found that a significant portion (41.7%) of the young doctors were moving aboard. Other studies came to a similar conclusion. A study found that 68% of the medical students wanted to move aboard.¹⁰ The reasons to move aboard included greater career opportunities, higher income and better health system.¹³⁻¹⁶ The vast number of doctors moving aboard creates a brain drain and depletes the number of doctors. This has led to an increased burden on an already overburdened system and increased the scarcity of doctors.

Our study found that many young doctors had decided to pursue the medical career prior to FSCE intermediate years. The reason for joining included helping others, due to parents' choice, research opportunity. Goel et al found similar reasons for joining medical school.¹⁶

The public vs private sector presents two different healthcare systems. Our study showed that more participants wanted to work in government as compared to the private sector [27.7% vs 21.1%]. Scott et al came to a similar conclusion.¹⁷ They found that more physicians wanted to work in the government sector. This

preference may be due to the job security, easy working hours and environment and low risk environment in the government sector.

CONCLUSION

The medical education system in Pakistan has shown a trend of increasing desire of the young doctor to move aboard. More focus showed be applied to this area. The brain drain that occurs in the form of medical graduates moving aboard needs to be addressed. Our study found that most believed that career counselling was helpful but only a small percentage availed such opportunity. Career counseling was significantly associated with clarity of mind and helps young doctors in making educated decisions. Measures such as making career counselling compulsory need to be taken.

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REFERENCES

1. Mandeville KL, Ulaya G, Lagarde M, Muula AS, Dzowela T, Hanson K. The use of specialty training to retain doctors in Malawi: A discrete choice experiment. *Soc Sci Med* 2016 Nov;169:109-118.
2. Mandeville KL, Bartley T, Mipando M. Future career plans of Malawian medical students: a cross-sectional survey. *Hum Resour Health* 2012;10:29-32.
3. Goudarzi H, Onozawa M, Takahashi M. Future career plans of medical students and the COVID-19 pandemic: Time to recover? *J Gen Fam Med* 2022;24:139-40.
4. Wiers-Jenssen J, Vaglum P, Ekeberg O. Kommende legers karriereplaner. Ambisjonsnivå og spesialiseringsplaner blant medisinstudenter [Career plans of future physicians. Level of ambition and plans for specialization among medical students]. *Tidsskr Nor Laegeforen* 1997;117:2807-11.
5. Riska E. Gender and medical careers. *Maturitas* 2011;68:264-7.
6. Winkel AF, Telzak B, Shaw J, Hollond C, Magro J, Nicholson J, et al. The Role of Gender in Careers in Medicine: A Systematic Review and Thematic Synthesis

- of Qualitative Literature. *J Gen Intern Med* 2021;36:2392-9.
7. Leonard JC, Ellsbury KE. Gender and interest in academic careers among first- and third-year residents. *Acad Med* 1996;71:502-4.
8. Custers EJ, Cate OT. Medical students' attitudes towards and perception of the basic sciences: a comparison between students in the old and the new curriculum at the University Medical Center Utrecht, The Netherlands. *Med Educ* 2002;36:1142-50.
9. Onakpoya OH, Onakpoya UU, Adereti GE. The prospect of anatomy as a career choice among clinical year medical students in Nigeria. *Ann Afr Med* 2009;8:90-4.
10. Zia S, Abbas M, Sulaiman M, Sheikh SM. Career Choices of Medical doctors at Graduate level - A Multicenter Study. *Pak J Med Sci* 2017;33:1086-90.
11. Goudarzi H, Onozawa M, Takahashi M. Impact of COVID-19 on international medical education and the future plans of medical students in Japan. *MedEd Publish* 2022;12:15.
12. Goudarzi H, Onozawa M, Takahashi M. Future career plans of medical students and the COVID-19 pandemic: Time to recover? *J Gen Fam Med* 2022;24:139-40.
13. Balouch MS, Balouch MM, Balouch MS, Qayyum W, Zeb Z. Career Aspirations of Junior Doctors in Pakistan: Exploring Reasons Behind The Brain Drain. *J Ayub Med Coll Abbottabad* 2022;34:501-6.
14. Sheikh A, Naqvi SH, Sheikh K, Naqvi SH, Bandukda MY. Physician migration at its roots: a study on the factors contributing towards a career choice abroad among students at a medical school in Pakistan. *Global Health* 2012;8:43-6.
15. Qureshi AZ, Rathore FA. Number of Pakistani physicians working abroad; do we really need to know? *J Pak Med Assoc* 2014;64:1410-2.
16. Goel S, Angeli F, Dhirar N, Singla N, Ruwaard D. What motivates medical students to select medical studies: a systematic literature review. *BMC Med Educ* 2018;18:16.
17. Scott A, Holte JH, Witt J. Preferences of physicians for public and private sector work. *Hum Resour Health* 2020;8:59063.

Development of learning models teeth brushing skills in early childhood; Is it needed?

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Objective: To analyses the need to develop a learning model for early childhood tooth brushing skills.

Methodology: This survey included head of schools, teachers, and parents. We used interview guidelines, questionnaires, and observation sheets. Tested the validity of instruments using Spearman Correlation statistical test and reliability with Alpha Cronbach. Qualitative data were analyzed triangulated; quantitative data by calculating mean values and presented descriptively.

Results: The study results show that 5-6-year-olds are qualified to be trained to brush their teeth

independently. The learning problem in early childhood schools was a lack of guidance, learning media, evaluation instruments and supporting facilities. Parents supported the development of learning models.

Conclusion: Developing a model for early childhood learning to brush teeth skills is urgently needed. The development is adapted to the characteristics of children aged 5-6 years to skillfully brush their teeth independently.

Keywords: Learning models, skills, brushing teeth, early childhood, preschool.

INTRODUCTION

Early childhood tooth damage is one of the problems in dental health that has not been addressed to date. Basic Health Survey results in Indonesia in 2018 average reached 8.1.¹ The high rate of tooth damage in children is due to the neglect of parents who assume that milk teeth will be replaced with permanent teeth.

A child aged 5-6 years begins learning to do things independently to prepare for primary school. One of them is to start self-training in personal hygiene.² The curriculum applied in early childhood learning has competencies clean and healthy living behavior, one of which is brushing teeth.³ Still, the high rate of tooth damage in early childhood suggests that the existing lessons are not adequate to train children to toothbrushing to prevent dental damage.

Providing early childhood toothbrushing skills is essential to care for the current milk teeth and to keep the permanent teeth that are beginning to grow healthy. Developing a learning model of tooth brushing skills can be one of the alternative solutions to addressing the high rate of dental damage in early childhood. Several studies were conducted about model of support for parents and teachers to change the behavior, interventions with a day and night program for 21 days, and impact of playful learning interventions on children's proper tooth-brushing behavior.⁴⁻⁶

However, previous studies have yet to develop a model of learning so that young children can brush their teeth

independently. Learning model development uses a set of theories, procedures and techniques that learning designers use to design, develop, evaluate and revise learning.⁷ This study aimed to develop a model of learning to brush teeth skills for early childhood by examining 1) the eligibility of 5-6-year-olds to be trained to clean their teeth independently, 2) the problems encountered in the learning of toothbrushing skills in early school education; and (3) the attitude of parents towards the development of a learning model of brushing tooth skills in school.

METHODOLOGY

This research used the mixed method. It was conducted at two early childhood education schools in Kelurahan Gandul, Cinere district, Depok City, West Java, involving two head schools, two teachers, and 56 parents of pupils.

The data were collected by conducting interviews with the heads of schools and teachers using the interview guidelines. We measured the attitude of parents using a Likert scale questionnaire of 7 statements, and observing ongoing learning to brush teeth with the observation sheet.

Statistical Analysis: We tested the validity of instruments using the Spearman Correlation statistical test (results between 0.302 and 0.780) and reliability with Alpha Cronbach (result was 0.668).

Table 1: Parents' attitude towards the development of a learning model of toothbrushing skills.

No	Statement	Very Disagree	Less Agree	Neutral	Agreed	Most Agree	Total
1	Children need to be trained in the technique of brushing the teeth	0	0	0	12	44	56
2	Age 5-6 years permanent teeth are still growing, it is important to train children to start brush teeth independently	0	3	6	28	19	56
3	Teaching the skills of toothbrushing in early childhood should be done in school because it is more focused and directed	1	10	19	22	4	56
4	Special learning strategies are needed involving schools and parents to co-train the child	1	2	8	22	23	56
5	Proper learning tools or media are needed to make it easier for the child to understand and practice tooth brush	0	3	7	27	19	56
6	Children need the accompaniment of parents when practicing the whole tooth surface at home	0	0	4	28	24	56
7	Milk teeth will be replaced with permanent teeth, children need to get trained to bridge teeth properly later after the tooth remains growing	25	21	0	6	4	56

Qualitative data from interviews and observation are triangulated analysis. Quantitative data from questionnaires sheets was analyzed by calculating mean values and presented descriptively.

RESULTS

The study included 56 people with age range of 3-7 years and mostly 5-6 years old (81,8%). The interviews showed that 5-6-year-old children are likely to be able to brush his teeth independently if well trained.

The problems faced in learning to brush teeth in schools were the lack of teaching materials such as guides for learning, not having a learning medium, not possessing an evaluation instrument and availability of sink is limited.

Measure parents' attitudes using the Likert Scale questionnaire (positive statements 1-6 and negative statements 7), with five answer options scores.

The data in Table shows that, most parents supported the importance of dental health in early childhood and the development of a learning model of brushing tooth

skills so that children can brush their teeth independently. The average value the result obtained of 4.15, included the category of parents agreed.

Based on observations of the learning activities of brushing the teeth skills carried out in school, teachers explain the purpose and stage of brushing teeth with a picture printed on paper, even at one school, without using media. Giving examples of brushing movements is done using only hand movements outside the mouth and needs to entirely mention which parts of the tooth surface should be brushed and the movements to be performed. Teaching the practice of brushing teeth is done in the schoolyard.

DISCUSSION

Reducing tooth damage in early childhood can be through learning. At ages 5 to 6, permanent teeth are starting to grow, so training to brush teeth independently is necessary. The age of 5-6 years is sufficiently stable in performing motor and physical movements. Thus, it is possible to train the technique of brushing teeth using

structured learning strategies, guided step by step, given reinforcement and positive feedback.

It is also supported by the research results, that preschool children who receive education in structured physical activity have significantly improved member coordination, cognitive development and complete tasks more accurately, in shorter time frames, improve concentration, independence and self-effectiveness through full attention and repetition.⁸⁻¹⁰

Regarding the motor physical development of 5-6-year-olds in their ability to brush their teeth, a related study found that there was no significant difference in dental hygiene between teeth brushed by parents and by children aged 5-7. It suggests that five-year-olds are likely to brush their teeth effectively when detailed information, supervision and motivation are given.¹¹

One of the learning strategies relevant to the goal of learning to brush teeth independently is Direct Instruction, teacher-led learning strategy to improve pupils' understanding of procedures, train pupils to perform complex behaviors that require accuracy of movement, break learning into smaller components, teachers directly simulate, guide and train students structured so that they can practice new skills independently.^{12,13}

Problems were found in early childhood school learning to brush teeth, indicates that the development of a learning model for toothbrushing skills is urgently needed because all of the problems can be overcome and is a stage in the evolution of the learning model unless the facility.

The learning model, is a system that has 10 (ten) stages, starting with identifying learning goals, learning analysis, analyzing learners, specific learning objectives, developing evaluation instruments, learning strategies, selecting and developing teaching materials, developing and implementing formative and summative evaluations.⁷ Based on the above stages, the development of a learning model, is ideally suited to addressing the problem of learning toothbrushing skills that schools face today.

Teaching a child's toothbrushing skills requires a learning medium that the child can observe and hold directly to provide a concrete experience. This aligns with Edgar Dale's concept of The Cone of Experience, which describes learning media as a link between making real experiences and the ability to understand symbols or abstract things.¹⁴

Early childhood has limitations in understanding abstract explanations, so real learning media in three dimensions/3D helps understand learning, especially related to brushing techniques and introduce tooth surfaces that need to be cleaned. This aligns with a

study, that only 14.5% respondents brush the entire surface of their teeth and tongue.¹⁵ 3D media can improve skills and shorten learning time for beginner students.¹⁶

Early childhood parents' attitudes mainly support the development of a model for learning to brush teeth in schools and that support will be constructive in achieving learning goals. The process of improving abilities accompanied by this teacher and parents is in line with the theory of the Zone of Proximal Development of Vygotsky, that potential skills can be enhanced into actual abilities with the guidance of an adult.¹⁷

The ultimate goal of developing a model is that children can brush their teeth independently and apply them consistently at home. Parental engagement in early childhood learning is an integral part of the success of a program.¹⁸ Children's skill learning scores increase as parents become more involved in school activities.¹⁹ Cultivate a sense of responsibility for their dental health to form good habits for dental health at an early age and in the future.

The limitations of this research are schools that are the data collection sites of only two schools. The more schools will be better to obtain increasingly comparative information related to the problems encountered in learning to brush teeth.

CONCLUSION

Developing a model for early childhood learning to brush teeth skills is urgently needed. The development is adapted to the characteristics of children aged 5-6 years to skillfully brush their teeth independently.

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REFERENCES

1. Kemenkes. Laporan Nasional Riskesdas 2018. Jakarta: Badan Penelitian dan Pengembangan Kesehatan; 2019. p196–205.
2. Kemendikbudristek. Capaian Pembelajaran untuk Satuan PAUD. Badan Standar, Kurikulum, dan Asesmen

- Pendidikan; 2022.
3. Kemendikbud. Kurikulum Tingkat Satuan Pendidikan (KTSP) Pendidikan Anak Usia Dini. Dirjen PAUD dan Pendidikan Masyarakat; 2018. p4–12.
 4. Purnama T, Ngatemi, Fadjeri I, Widiyastuti R. Model mentoring teachers and parents as an efforts for brushing teeth behavior in preschool children. *Indian J Forensic Med Toxicol.* 2020;14(4):3511–6.
 5. Melo P, Fine C, Malone S, Taylor S. Impact of the Brush Day & Night Programme on Well-Being, Plaque, and Dental Caries in Children. *Int Dent J.* 2021;71:S15–30.
 6. Akkaya DD, Sezici E. Teaching Preschool Children Correct Toothbrushing Habits Through Playful Learning Interventions: A Randomized Controlled Trial. *J Pediatr Nurs.* 2021;56:e70–6.
 7. Dick W, Carey L, Carey JO. *The Systematic Design of Instruction.* United States of America: Pearson Education Inc.; 2015. p6–27.
 8. Ruiz-Esteban C, Andrés JT, Méndez I, Morales Á. Analysis of motor intervention program on the development of gross motor skills in preschoolers. *Int J Environ Res Public Health.* 2020;17(13):1–12.
 9. Buzescu R, Nechita F, Cioroiu SG. The relationship between neuromuscular control and physical activity in the formation of the visual- psychomotor schemes in preschools. *Sensors (Switzerland).* 2021;21(1):1–10.
 10. Bush D, Sciaraffa M. “I Can Do It!”: Supporting Young Children’s Joy and Independence Through Practical Life Exercise in a Non-Montessori Classroom. *Dimens Early Child.* 2019;47(1):22–4.
 11. Ozgul BM, Sakaryali D, Senirkentli GB, Tirali RE, Cehreli SB. Do really parents brush their children’s teeth better? *Eur J Paediatr Dent.* 2019;20(4):325–9.
 12. Kilbane CR, Milman NB. *Teaching Models Designing Instruction for 21st for Century Learners.* New Jersey: Pearson Education. Inc; 2014. p121–139.
 13. Joyce B, Weil M, Calhoun E. *Models of teaching.* Vol. Ninth Edit. New Jersey: Pearson; 2015. p5–346.
 14. Richey RC, Klein JD, Tracey MW. *The Instructional Design Knowledge Base.* New York: Routledge Taylor & Francis Group; 2011. p8–95.
 15. Eigbobo JA, Arigbede AO. Tooth brushing skills and oral hygiene practices in a selected group of Nigerian children. *Afr J Med Med Sci.* 2020;49(6):95–102.
 16. Chae YK, Lee H, Jih MK, Lee HS, Lee JW, Kim SH, et al. Validation of a three-dimensional printed model for training of surgical extraction of supernumerary teeth. *Eur J Dent Educ.* 2020;24(4):637–43.
 17. Qin L. The “wrong Love” between the Zone of Proximal Development and Scaffolding: An Interview with Prof. James P. Lantolf. *Chinese J Appl Linguist.* 2022;45(1):138–49.
 18. Varshney N, Lee S, Temple JA, Reynolds AJ. Children and Youth Services Review Does early childhood education enhance parental school involvement in second grade?: Evidence from Midwest Child-Parent Center Program. *Child Youth Serv Rev.* 2020;117(July):105317.
 19. Jeon H joo, Peterson CA, Luze G, Carta JJ, Clawson C. Children and Youth Services Review Associations between parental involvement and school readiness for children enrolled in Head Start and other early education programs. *Child Youth Serv Rev.* 2020;118(August):105353.

Frequency and type of tobacco consumption in oral squamous cell carcinoma patients and its association with age and gender

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Objective: To investigate the frequency and type of tobacco in oral Squamous Cell Carcinoma (OSCC) patients and its association with age and gender.

Methodology: This questionnaire based descriptive study was conducted at Al-Mustafa Medical Center, Karachi from Jan 2023 till June 2023.

Results: Out of 138 patients, 80.4% were male with an average age of 46.18±11.97 years. Significant age-related associations were observed, particularly among the 20-30 and 31-40 age groups. Significant gender associations were noted for pan, gutka, and smoking,

indicating strong male predominance.

Conclusion: Onset of OSCC is high in young patients signifying a noteworthy change in age distribution towards a younger demographic. Also, consumption of specific tobacco like pan, gutka, and smoking was strongly associated with male gender, highlighting the essentiality of targeted interventions to curb the escalating OSCC risk associated with chewable tobacco.

Keywords: Oral squamous cell carcinoma, chewing tobacco, oral mucosa.

INTRODUCTION

Oral cavity carcinoma is one of the most frequent and life-threatening malignant tumors with a constant increasing incidence globally.¹ Oral Squamous Cell Carcinoma (OSCC) originates from mucosa of oral cavity and can involve adjacent buccal mucosa. While several risk factors contribute to OSCC, such as low socioeconomic status, poor dental hygiene, inadequate diet, viral infections, ill-fitting dentures or chipped teeth, the etiology of OSCC is intricate. Tobacco use, whether through smoking or other forms, remains the foremost reported risk factor.²⁻⁴

Majority of people are unaware that tobacco contains more than 60 dangerous compounds, including carcinogens.⁴ Every year, 2.5% of all newly reported carcinoma cases are of OSCC while the death rate is 1.9% globally.⁵ In Pakistan, OSCC is the second most common malignancy leading to mortality and is almost 5 times higher as compared to global incidence (3.8%).^{1,6} Several factors contribute to rising incidence of OSCC including genetics, alcohol and tobacco consumption.⁷ In South Asian countries, OSCC is primarily associated with tobacco usage along with other snuffing materials.⁸ In South Asia, chewable tobacco is more common than smoking tobacco, maybe due to easy availability, low cost and cultural norms. Chewing tobacco habits are common among young particularly females.⁹ These practices are further reinforced by illiteracy and ignorance of their harmful consequences.¹⁰ Chewable

tobacco leads to production of reactive oxygen species (ROS) and free radicals which damage the DNA and RNA, leading to carcinogenicity.³ While gender-based assessments of OSCC risk factors have been conducted in some regions, there is a notable gap in such researches in Karachi having high prevalence of chewable tobacco habits.¹¹ Hence, the focus of this study was to investigate the frequency and types of tobacco among OSCC patients and its association with age and gender.

METHODOLOGY

This cross-sectional study was conducted at Al-Mustafa Medical Center, Karachi from Jan 2023 till June 2023 after acquiring (IRB:11/23/KIMS) from Karachi Institute of Medical Sciences. We used convenience probability sampling. Sample size 138 was determined using WHO sample size calculator (95% confidence level and an absolute precision of 0.07).¹² Patients included were diagnosed cases of OSCC based on histopathological examinations. Patients having cancer other than OSCC, undergoing cancer treatment, having cardiac or hepatic disease, pregnancy or lactation were excluded.

Data were collected using a pre-structured questionnaire after written informed consent. It included details related to demographic information, medical history, and tobacco habits. To enhance the questionnaire's reliability, a rigorous validation process was implemented on samples of 10 patients, likely representative of study population. Internal consistency of each question was

assessed using Cronbach's alpha. Questions achieving Cronbach's alpha score >90 were deemed highly reliable, subsequently incorporated into final questionnaire.

Statistical Analysis: Data were analyzed using SPSS version 26. The association between tobacco with gender and age was assessed using the Chi-square test. $p < 0.05$ was considered significant.

RESULTS

Out of 138 participants, majority were male (80.4%) with average age of 46.18 ± 11.97 years. Most were in 31-40 age range, majority were married (87%) and Urdu speaking (66.7%) (Table 1).

Significant gender associations were observed for Gutka, Pan, and Smoking ($p = 0.001$) (Table 2). Naswar, Gutka,

Betel nut, Pan, and smoking showed significant association ($p < 0.001$) with 20-30 and 31-40 age groups (Table 3).

Table 2: Association of gender with tobacco products.

Tobacco Product	Female	Male	p-value
Naswar	11	51	0.621
Gutka	3	61	<0.001
Betel nut	14	49	0.671
Pan	18	56	0.001
Smoking	0	32	0.001

Table 1: Demographic distribution of participants.

Demographic Characteristics	Number	%
Gender		
Male	111	80.4%
Female	27	19.6%
Age distribution		
20-30	16	11.6%
31-40	38	27.5%
41-50	33	23.9%
51-60	34	24.6%
>60	17	12.3%
Marital status		
Married	120	87%
Unmarried	18	13%
Ethnicity		
Balochi	11	8.0%
Punjabi	4	2.9%
Pathan	6	4.3%
Sindhi	6	4.3%
Saraiki	2	1.4%
Urdu speaking	92	66.7%
Others	17	12.3%

DISCUSSION

Majority of studies opted to uniformly designate individuals <40 as distinct group for OSCC.^{13,14} The lack of consensus and ongoing controversy, particularly in the context of oral cancer among young non-tobacco users, raises questions about whether these distinct etiological factors result in characteristic clinical and progressive behaviors compared to older patients.¹⁵

Present study revealed the OSCC onset in young individuals (in 20s). This early onset aligns with another study, indicating shift in age distribution of OSCC towards younger demographics.⁵ In contrast, previous studies reported mean age in 50s and 60s.⁵ In Europe, the mean age of OSCC, previously 63 years, has now declined to forties, showing concerning global trend towards younger ages.^{16,17}

In present research, the prevalence of pan consumption was higher in 41-50 and 51-60, closely aligning with a previous study, where male gender was primary demographic in 36-42 years individuals.¹⁸ Current analysis highlights that smokeless tobacco was more common form, aligning with a previous investigation, emphasizing the significant role of smokeless tobacco in OSCC pathogenesis, particularly in young individuals. This could be attributed to economic factors, and smokeless tobacco being perceived as a safer substitute for smoking.¹⁹

Globally, OSCC is predominantly observed in males showing male-to-female ratios of 4:1 to 3:2.^{20,21} This discrepancy is likely influenced by greater tendency of males in engaging smoking compared to females.²² In Pakistan, where smoking and alcohol consumption carry more stigma for females, amplifies the existing gender disparity in OSCC prevalence.²³ In our study, OSCC was more common in males whereas gutka was most common

Table 3: Association of age with tobacco products.

Age Group	Naswar	Gutka	Betel nut	Pan	Smoking	p-value
20-30	9 (6.5%)	9 (6.5%)	9 (6.5%)	6 (4.3%)	6 (4.3%)	<0.001
31-40	27 (19.6%)	29 (21.0%)	23 (16.7%)	18 (13.0%)	10 (7.2%)	<0.001
41-50	11 (8.0%)	10 (7.2%)	11 (8.0%)	15 (10.9%)	1 (0.7%)	0.126
51-60	8 (5.8%)	8 (5.8%)	14 (10.1%)	23 (16.7%)	9 (6.5%)	0.990
>60	7 (5.1%)	8 (5.8%)	6 (4.3%)	12 (8.7%)	6 (4.3%)	0.588

chewing tobacco, this is in accordance with past studies.^{1,5,6,24}

CONCLUSION

Present study revealed young onset of OSCC, signifying change in age distribution. Notably, there were significant gender associations, showcasing male predominance for specific tobacco forms. This emphasizes the need for targeted interventions to tackle the increasing prevalence of OSCC in youth.

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REFERENCES

1. Aqeel R, Aslam Z, Amjad A. Examine the Prevalence of Oral Squamous Cell Carcinoma Also Determine the Risk Factors and Causes of Improper Diagnosis. *P J M H S* 2017;13:833-5.
2. Sreelatha SV, Shetty S, Karnaker VK, Chowdhury CR. Patterns of Tobacco Consumption among Oral Squamous Cell Carcinoma Cases Attending a Tertiary Care Dental Hospital in Coastal Karnataka of India. *World J Dent* 2019;10:350-3.
3. Jiang X, Wu J, Wang J, Huang R. Tobacco, and oral squamous cell carcinoma: A review of carcinogenic pathways. *Tob Induc Dis* 2019;17:29-32.
4. Samim D, Mean M, Clair C, Marques-Vidal P. A 10-year observational study on trends and determinants of smoking status. *PLoS One* 2018;13:e0200010.
5. Yasin MM, Abbas Z, Hafeez A. Correlation of histopathological patterns of OSCC patients with tumor site and habits. *BMC Oral Health* 2022;22:305.
6. Mubarak S, Akbar S, Devi B, Tariq U, Junaid A. Demographic Spectrum of Oral Squamous Cell Carcinoma in Public Health Care Facility in Karachi Pakistan. *Pak J Med Health Sci* 2022;16:505-7.
7. Madathil S, Rousseau MC, Joseph L, Coutlée F, Schlecht NF, Franco E, et al. Latency of tobacco smoking for head and neck cancer among HPV-positive and HPV-negative individuals. *Inter J Cancer* 2020;147:56-64.
8. Boceila E, Atef A, Hassan M, Ali M, Khalele BA, Shaban M. Epidemiology of orofacial malignancies in Egypt (2016-2021): A reappraisal account. *Advan Clin Exp Dent* 2022;2:24-36.
9. Gupta AK, Kanaan M, Siddiqi K, Sinha DN, Mehrotra R. Oral cancer risk assessment for different types of smokeless tobacco products sold worldwide: A review of reviews and meta-analyses. *Can Prev Res* 2022;15:733-46.
10. Majid A, Rathi SL, Fahim A, Batool S, Iqbal W, Shankar B. Types of Various Oral Mucosal Lesions with Respect to Trends of Chewable Tobacco and Their Subsequent Histopathological Findings: Histopathology of Oral Mucosal Lesions. *J Islamic Int Med Coll* 2022;17:245-9.
11. Perveen F, Baig S, Ahmad F, Majeed N. Detecting human papillomavirus 6 & 11 in a set of Pakistani population. *Brit J Medic Med Res* 2016;17:1-9.
12. Ullah A, Pervez N, Javaid MM, Din SU, Liaqat S, Junaid M. Assessment of the Influence of Risk Factors on the Incidence of Oral Squamous Cell Carcinoma (OSCC) in the Northern Pakistani Population. *Pak J Public Health* 2023;13:80-3.
13. Johnson DE, Burtneess B, Leemans CR, Lui VW, Bauman JE, Grandis JR. Head, and neck squamous cell carcinoma. *Nat. Rev Dis Primers* 2020;6:92-5.
14. Teixeira LR, Almeida LY, Silva RN, Mesquita AT, Colturato CB, Silveira HA, et al. Young and elderly oral squamous cell carcinoma patients present similar angiogenic profile and predominance of M2 macrophages: Comparative immunohistochemical study. *Head Neck* 2019;41:4111-20.
15. Abdulla R, Adyanthaya S, Kini P, Mohanty V, D'Souza N, Subbannayya Y. Clinicopathological analysis of oral squamous cell carcinoma among the younger age group in coastal Karnataka, India: A retrospective study. *J Oral Maxil Pathol* 2018;22:180-7.
16. Sahaf R, Naseem N, Anjum R, Nagi A. Oral squamous cell

- carcinoma: A clinicopathologic study. *Pak Oral Dent J* 2017;37:49-53.
17. Serra A, Caltabiano R, Scalia G, Palmucci S, Di Mauro P, Cocuzza S. Papillary squamous cell carcinoma of the palatine tonsil: a rare cancer of the head and neck. *Acta Otorhinolaryngologica Italica* 2017;37:341-5.
18. Thangavelu RP, Mohan KR, Fenn SM, Appusamy K. Evaluation of nicotine dependence among smokeless tobacco users using the Fagerstrom Nicotine Dependence Scale for smokeless tobacco. *Cureus* 2023;15:e38639.
19. Campbell BR, Sanders CB, Netterville JL, Sinard RJ, Rohde SL, Langerman A, et al. Early onset oral tongue squamous cell carcinoma: associated factors and patient outcomes. *Head Neck* 2019;41:1952-60.
20. Lee YC, Young CK, Chien HT, Chin SC, Iandelli A, Liao CT, et al. Characteristics and outcome differences in male and female oral cavity cancer patients in Taiwan. *Medicine* 2021;100:e27674.
21. Alshehri BM. Trends in the incidence of oral cancer in Saudi Arabia from 1994 to 2015. *World J Surg Oncol* 2020;18:1-6.
22. Bouckaert M, Munzhelele TI, Feller L, Lemmer J, Khammissa RA. The clinical characteristics of oral squamous cell carcinoma in patients attending the Medunsa Oral Health Centre, South Africa. *Integr Cancer Sci Therap* 2016;3:575-8.
23. Kanwal M, Haider G, Zareef U, Saleem S. Addiction of tobacco chewing and smoking in the patients of head and neck squamous cell carcinoma: A descriptive epidemiological study in Pakistan. *Pak J Med Sci* 2019;35:1712-6.
24. Mehdi RF, Shaikh F, Baig S, Qureshi MF, Lakhani M, Zia I, et al. Oral squamous cell carcinoma and tobacco use. *J Adv Med Res* 2018;28:1-5.

Relationship between demographic characteristics and motivational factors among healthcare providers at a secondary care hospital in Karachi, Pakistan

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Objective: To investigate the potential effect among gender regarding salary, recognition, rewards and other potential benefits, and job title on motivation, recognizing the ability to introduce distinct patterns within the medical profession.

Methodology: This cross-sectional study used convenience sampling technique and was carried out from July 2022 and January 2023. The study included healthcare professionals such as doctors, nurses, and paramedics and data were gathered using a questionnaire. Data were analyzed using SPSS software.

Results: The salary, acknowledgment, job challenges,

and rewards were important motivators for healthcare workers. The gender had no significant effect on these motivational factors, but educational background played a significant role.

Conclusion: The motivation of employees is essential for the efficient functioning of healthcare institutions and the delivery of high-quality services. This motivation is reinforced by a challenging job, job recognition, reward, financial incentives, and other benefits.

Keywords: Motivational factors, gender, designation, healthcare providers.

INTRODUCTION

Motivation is the driving force that determines how much effort an individual is willing to invest in achieving the goals of their organization. Individuals driven by motivation frequently attain heightened levels of performance, thereby enhancing organizational efficiency.¹ The satisfaction of three pivotal conditions is often deemed essential for fostering employee motivation: a sense of purpose, a sense of responsibility, and an understanding of the outcomes. It is noteworthy that a strong correlation exists between the motivation of healthcare professionals and the overall quality of healthcare services provided.²

Motivation is the stimulus behind organizational goals, and it is affected by a complex interplay of external factors like rewards and internal factors like self-concept and personal needs.^{3,4} Health care provider motivation is a complex and critical factor that has an important effect on the provision of healthcare services.⁵ Recognizing the factors that drive healthcare professionals' motivation is critical, as it improves their well-being and increases the overall efficiency of healthcare systems.⁶

Healthcare systems in developing countries, such as Pakistan, face challenges due to a lack of employee motivation and a shortage of healthcare professionals.⁷ Improving staff motivation and performance is critical for overcoming challenges.⁸ This entails using a combination of financial and non-financial incentives to

improve healthcare delivery in these areas.⁹ Human Resources plays an essential role in creating a supportive healthcare environment.^{10,11} Furthermore, motivation among healthcare workers is strongly related to demographic factors such as age, gender, and education, as these characteristics provide valuable insights into what motivates healthcare workers on a daily basis.¹² This study aimed to explore the impact of gender and job designation on motivation within the healthcare workforce.

METHODOLOGY

The study was conducted in secondary care hospitals in Karachi and included health professionals. It had a sample size of 450 potential participants, with 380 respondents, and followed a six-month cross-sectional study design from July 2022 to January 2023. All the respondents were from the same institute. Reminders were sent periodically, at an interval of 15 days.

Healthcare professionals, including doctors, nurses, paramedical staff and individuals with a minimum of one year of employment within the organization were included in the study. Those who declined to provide consent were excluded from the study. Convenience sampling technique was employed, facilitating a quicker and more cost-effective data collection process.

A 28-item questionnaire, administered through Google Forms was used. This approach facilitated efficient and

convenient participation, allowing respondents to engage electronically. Google Forms streamlined the process and enabled easy tracking and analysis of the collected data. A pilot study involving 5 administrative employees was conducted prior to data collection to ensure the face validity of the questionnaire. The final questionnaire was self-administered by the respondents.

Statistical Analysis: Data were analyzed using SPSS version 26. chi-square tests were conducted to identify associations between categorical variables. Cronbach's alpha coefficients were employed for the purpose of examining internal data consistency. $p < 0.05$ was considered statistically significant.

RESULTS

Table 1 presents demographic, qualification, designation, experience, and salary data for a diverse group of individuals, reflecting various ages, qualifications, and salary levels, encompassing healthcare professionals with differing experience and responsibilities. Key motivational factors are shown in Table 2. Correlation between gender and motivational factors is presented in Table 3.

Dental Officers primarily cited a high salary (86%) as their primary motivation, while Medical Officers and Consultants balanced motivators, focusing on job recognition (45% and 19.2% respectively). Nursing Staff have diverse motivations, with 29.5% highlighting a high salary. The statistically significant variations ($p < 0.001$) underscore the need for tailored incentive strategies in the healthcare sector, depending on job roles, as illustrated in Table 4.

Table 1: Demographics characteristics of study participants.

Demographics	Number	%
Gender		
• Male	132	34.7%
• Female	242	63.7%
Age (years)		
• < 18	13	3.4%
• 8-29	218	57.4%
• 30-45	131	34.5%

• 46-50	11	2.9%
• > 50	7	1.8%
Qualification		
• Matriculation	47	12.4%
• Intermediate	77	20.3%
• Under graduate	28	7.4%
• Graduate	165	43.4%
• Post graduate	63	16.6%
Designation		
• Nursing staff	132	34.7%
• Medical officer	40	10.5%
• Resident medical officer	59	15.5%
• Dental officer	86	22.6%
• Senior medical officer	37	9.7%
• Consultant	26	6.8%
Experience (in years)		
• < 1	56	14.7%
• 1-2	137	36.1%
• 2-5	71	18.7%
• > 5	115	30.3%
Salary (In Pkr)		
• <50000	208	54.7%
• 50000-100000	106	27.9%
• 100000-200000	32	8.4%
• 200000-300000	7	1.8%
• >300000	27	7.1%

Table 2: Key motivational factors among study participant.

Motivation Factor	Number	%
High salary	154	40.5
Challenging job	69	18.2
Job recognition	70	18.4
Rewards	33	8.7
Other benefits		
• Happy with work environment	54	14
• Patient served		
• Perceived facilities		
• Relationship with co-workers		

Table 3: Correlation between gender and motivational factors.

Gender	High Salary		Challenging Job		Job Recognition		Rewards		Other Benefits		p-Value
	N	%	N	%	N	%	N	%	N	%	
Male	54	40.9	25	18.9	23	17.4	15	11.4	14	10.6	0.169
Female	100	41.3	44	18.2	44	18.2	17	7	37	15.3	

Table 4: Correlation between designation and motivational factors.

Designation	High salary		Challenging job		Job Recognition		Rewards		Other Benefits		p-Value
	N	%	N	%	N	%	N	%	N	%	
Nursing Staff	39	29.5	23	17.4	18	13.6	14	10.6	37	28	<0.001
Medical Officer	9	22.5	11	27.5	18	45.0	1	2.5	1	2.5	
Resident Medical Officer	15	25.4	14	23.7	18	30.5	8	13.6	15	25.4	
Dental officer	74	86.0	6	7.0	1	1.2	2	2.3	3	3.5	
Senior Medical Officer	8	21.6	9	24.3	10	27.0	3	8.1	7	18.9	
Consultant	9	34.6	6	23.1	5	19.2	5	19.2	1	3.8	

DISCUSSION

Encouraging employees in healthcare organizations to identify and address motivating variables is critical for effective management practices and the provision of productive, high-quality medical care.¹³ Our research underscores that healthcare workers are strongly driven by incentives like competitive salaries, rewards, and challenging roles, leading to their satisfaction, particularly in economically disadvantaged areas and playing a role in healthcare professionals' migration from developing nations to more economically advanced ones.¹⁴ A study from Pakistan also suggests a noteworthy positive correlation between employee participation, performance appraisal, and job satisfaction.¹⁵

The results of this study indicate that there is no statistically significant association between gender and motivation. This is in contrast to a study from Cyprus, where female doctors reported notably higher motivation regarding remuneration factors compared to male colleagues.¹⁶ The variation in motivation factors may be linked to socio-political system disparities in the study regions and differs from another study in Addis Ababa hospitals, which identified age as a crucial factor in nurse motivation.¹⁷

In our investigation, both dentists and nursing staff emphasized the critical role of financial incentives, such as competitive wages and incentives in motivating healthcare professionals and meeting basic needs such as housing and living expenses, which is consistent with extensive studies from multiple countries.^{16,18-20} Hesampour et al, reported lowest level of job satisfaction among academic staff in Iran which was associated with their salaries and wages.²¹ This underscores the significance of decent salaries in meeting survival needs and enhancing motivation, leading to increased productivity levels.

Our study found that medical officers experience a lack of job recognition, as a previous research highlighted the significant connection between recognition and staff motivation.²² Ayalew et al. emphasized the importance of job recognition for boosting job satisfaction and motivation, while incentives, in various forms, prove highly effective in inspiring goal achievement, productivity, and accomplishments.²³

Possible study limitations include social desirability bias in responses, concerns about information confidentiality affecting honesty, and a limited focus on variables. These limitations underscore the importance of interpreting findings within the context of these constraints and highlight avenues for further investigation and methodological refinement.

CONCLUSION

The study emphasizes the significance of recognizing various motivations among health care workers, such as financial incentives, job challenges, recognition, and other benefits. This comprehension is critical for healthcare organizations seeking to establish encouraging workplaces that meet the various requirements of their workforce.

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REFERENCES

1. Lăzăroiu G. Employee motivation and job performance. *Linguit Philop Invest* 2015;97-102.
2. Krstic M, Obradovic V, Terzic-Supic Z, Stanisavljevic D, Todorovic J. Motivational factors of employees in health care institutions in Serbia. *Management: J Sustainable Business Management Solutions Emerging Economies* 2019;24:33-43.
3. Shkoler O, Kimura T. How does work motivation impact employees' investment at work and their job engagement? A moderated-moderation perspective through an international lens. *Front Psychol* 2020;11:38.
4. Dagne T, Beyene W, Berhanu N. Motivation, and factors affecting it among health professionals in the public hospitals, Central Ethiopia. *Ethiop J Health Sci* 2015;25:231-42.
5. Wang H, Jin Y, Wang D, Zhao S, Sang X, Yuan B. Job satisfaction, burnout, and turnover intention among primary care providers in rural China: results from structural equation modeling. *BMC Fam Pract* 2020;21:1-10.
6. Nilsen P, Seing I, Ericsson C, Birken SA, Schildmeijer K. Characteristics of successful changes in health care organizations: an interview study with physicians, registered nurses and assistant nurses. *BMC Health Ser Res* 2020;20:1-8.
7. Karamat J, Shurong T, Ahmad N, Afridi S, Khan S, Khan N. Developing sustainable healthcare systems in developing countries: examining the role of barriers, enablers and drivers on knowledge management adoption. *Sustainability* 2019;11:954.
8. Schuster RC, de Sousa O, Rivera J, Olson R, Pinault D, Young SL. Performance-based incentives may be appropriate to address challenges to delivery of prevention of vertical transmission of HIV services in rural Mozambique: a qualitative investigation. *Hum Res Health* 2016;14:1-15.
9. Kok M, Abdella D, Mwangi R, Ntinginya M, Rood E, Gassner J, et al. Getting more than "claps": incentive preferences of voluntary community-based mobilizers in Tanzania. *Hum Res Health* 2019;17:1-9.
10. El-Gazar HE, Zoromba MA. Nursing human resource practices and hospitals' performance excellence: the mediating role of nurses' performance. *Acta Bio Medica: Atenei Parmensis* 2021;29;92(S2):e2021022.
11. Vo TTD, Tuliao KV, Chen C-W. Work motivation: The roles of individual needs and social conditions. *Behav Sci* 2022;12:49.
12. Nasreen S, Shah M. Effect of selected demographic variables on teacher motivation in secondary schools of Lahore, Pakistan. *Pak J Educ Res* 2021;4:291-301.
13. Chmielewska M, Stokwizewski J, Filip J, Hermanowski T. Motivation factors affecting the job attitude of medical doctors and the organizational performance of public hospitals in Warsaw, Poland. *BMC Health Serv Res* 2020;20:1-12.
14. Ghimire J, Kumal A, Mahato R, Gupta R. Factors associated with the motivation and de-motivation of health workforce in Nepal. *J Nepal Health Res Council*. 2013. doi.org/10.33314/jnhrc.v0i0.374
15. Alkhateri AS, Abuelhassan AE, Khalifa GS, Nusari M, Ameen A. The Impact of perceived supervisor support on employee's turnover intention: The Mediating role of job satisfaction and affective organizational commitment. *Int Bus Manag* 2018;12:477-92.
16. Lambrou P, Kontodimopoulos N, Niakas D. Motivation, and job satisfaction among medical and nursing staff in a Cyprus public general hospital. *Human Res Health* 2010;8:1-9.
17. Negussie N. Relationship between rewards and nurses' work motivation in Addis Ababa hospitals. *Ethiop J Health Sci* 2012;22:107-112.
18. Grytten J. Payment systems and incentives in dentistry. *Comm Dent Oral Epidemiol* 2017;45:1-11.
19. Amiresmaeli M, Jamebozorgi MH, Jamebozorgi AH. Identifying factors affecting dentists' retention in deprived areas in Iran. *Int J Health Plann Manage* 2022;37:1340-50.
20. George A, Bhatnagar A, Alonge K, Gupta S. Primary healthcare workers' views of motivating factors at individual, community and organizational Levels: A qualitative study from Nasarawa and Ondo States, Nigeria. 2017.
21. Hesampour M, Akbari M, Khanjani N, Naghibzadeh-Tahami A, Dehghan A, Nabi pour AR, et al. Job satisfaction among academic staff: A cross-sectional study. *Int J Occup Hyg* 2016;8:129-35.
22. Daneshkohan A, Zarei E, Mansouri T, Maajani K, Ghasemi MS, Rezaeian M. Factors affecting job motivation among health workers: a study from Iran. *Glob J Health Sci* 2015;7:153-7.
23. Ayalew F, Kibwana S, Shawula S, Misganaw E, Abosse Z, Van Roosmalen J, et al. Understanding job satisfaction and motivation among nurses in public health facilities of Ethiopia: a cross-sectional study. *BMC Nursing* 2019;18:1-13.

Comparison of nigella sativa and pioglitazone on hyperglycemia, adiponectin and resistin in streptozotocin induced diabetic mice

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Objective: To compare the effects of nigella sativa and pioglitazone on hyperglycemia, hyperlipidemia, adiponectin and resistin in streptozotocin induced diabetic mice.

Methodology: This quasi-experimental study was conducted from June 2021 to May 2022. Thirty mice were obtained. Fifteen were included in each of the two groups. Mice were given high fat diet for 8 weeks followed by low dose of streptozotocin injection intraperitoneally. After confirmation of diabetes, mice were enrolled for further study. Nigella sativa and pioglitazone in doses of 300 mg/kg and 30mg/kg were given by gavage tube once daily for 16 weeks. Blood glucose, adiponectin, resistin, cholesterol and

triglycerides levels were observed after 16 weeks in both the groups. Statistical analyses were done by SPSS version 20.

Results: There were statistically significant changes in blood glucose, adiponectin, resistin, cholesterol and triglycerides levels in diabetic mice given pioglitazone as compared to those who received nigella sativa ethanolic extraction ($p < 0.001$).

Conclusion: Pioglitazone significantly improved hyperglycemia, dyslipidemia, adiponectin and resistin in high fat diet, streptozotocin induced diabetic mice in comparison to nigella sativa ethanolic extraction.

Keywords: Diabetes mellitus, adipokines, thiazolidinediones.

INTRODUCTION

Obesity is a prevalent metabolic disease characterized by excess accumulation of white adipose tissue (AT) due to increased food intake and changes in lifestyle.¹ AT is the largest endocrine organ by secreting hundreds of hormones and cytokines, which act at both autocrine/paracrine and endocrine level. AT produces a variety of pro-inflammatory and anti-inflammatory hormones called adipokines, leptin, resistin, adiponectin, adipolin, visfatin, and omentin as well as cytokines such as tumor necrosis factor- α (TNF- α), interleukin-6 (IL-6), pigment epithelium-derived factor (PEDF), and progranulin (PGRN).²

Adipokines participate in the regulation of glucose and lipid metabolism, energy homeostasis, feeding behavior, insulin sensitivity, inflammation, immunity, adipogenesis, vascular function and coagulation.³ Pro-inflammatory hormones produced by AT result in insulin resistance and obesity and the increased risk of cardiovascular disease, whereas anti-inflammatory and insulin-sensitizing adipokines including adiponectin, adipolin, and omentin act vice versa.^{4,5} Resistin is an adipose tissue and macrophage derived hormone and exerts its effects on both inflammatory and insulin signaling pathways and its raised levels are associated with insulin resistance and type 2 Diabetes Mellitus

(DM).⁶

Pioglitazone selectively stimulates PPAR- γ and to a lesser extent PPAR- α . It modulates the transcription of the insulin-sensitive genes involved in the control of glucose and lipid metabolism in the muscle, adipose tissue, and the liver.⁷ It decreases the level of triglycerides and increases that of high-density lipoproteins (HDL) without changing low-density lipoproteins (LDL) and total cholesterol in patients with disorders of lipid metabolism.⁸

Nigella sativa is a widely used medicinal plant throughout the world. It is very popular in various traditional systems of medicine like Unani and Tibb, Ayurveda and Siddha.⁹ Nigella sativa seed ethanol extract (NSEE) exhibits the remarkable ability in vitro to concomitantly increase insulin secretion, induce proliferation of pancreatic β cells, and stimulate glucose uptake in skeletal muscle and fat cells. It is postulated NSEE may exert its antidiabetic effect through AMP-kinase (AMPK) dependent signaling, Glut4 protein content and adipokines.¹⁰

Pioglitazone exerts its antidiabetic effects through raised adiponectin and decreased resistin levels. The effects of Nigella sativa on adiponectin and resistin levels have not been studied. Limited work on this aspect compelled us to compare the effects of nigella sativa and pioglitazone

on hyperglycemia, hyperlipidemia, adiponectin and resistin in streptozotocin induced diabetic mice.

METHODOLOGY

This quasi-experimental study was carried out at Department of Physiology, Al-Nafees Medical College and Hospital Islamabad, in collaboration with National Institute of Health (NIH), Islamabad from June 2021 to May 2022. Sample size was calculated by using WHO sample size calculator by using statistics from study of Ahmed et al.⁸ Ethical approval was granted by ethical committee.

Healthy BLAB/C mice were procured from the animal house of NIH Islamabad. These animals were bred at the NIH and were used in the experiment. They were adult male mice 60 days old weighing 25gms±5gms. Animals were handled a week before the start of the study to acclimatize them to new handlers. The experimental period consisted of 24 weeks divided in two phases.

All mice were given feed mixed with cholesterol (Applichem, Dermstadt, Germany. CAT No. A08070100) at a dose of 400mg/kg body weight, along with banaspatti ghee 310 g/kg body weight. This diet continued for 8 weeks.¹¹ After 8 weeks, all mice were kept fasted for 8 hours. All mice were given injection Streptozotocin 35mg/kg intraperitoneally dissolved in citrate buffer.¹² After one week of STZ injection, mice were kept fasted for 12 hours and diabetes was confirmed by measuring blood glucose levels in blood samples from the tail vein with a One Touch Glucometer (Life scan; Johnson & Johnson, New Brunswick, NJ, USA). Mice with blood glucose levels 200mg/dl or more were considered diabetic.¹³

The intervention period consisted of 16 weeks. The mice were divided into two groups. Group I had Nigella sativa solution and group II had with Pioglitazone solution given once daily in morning with gavage tube for 16 weeks. During intervention period, mice were given treatment as follows: Group I mice were given ethanolic extraction of Nigella Sativa in a dose of 300 mg/kg by gavage tube once in the morning¹⁴ while group II mice were given pioglitazone 30 mg/kg by gavage tube once in morning.

After 16 weeks of intervention, blood glucose levels were estimated after overnight fasting from the tail vein with a One Touch Glucometer. After blood glucose estimation, intracardiac sampling was done. Estimation of adiponectin levels was done by Mouse adiponectin Elisa Kit by Assaypro, Catalogue No: ERA2500-1. Estimation of Resistin levels was done by Mouse resistin Elisa kit by Assay Pro, Catalogue no: EMR1001-1. Serum cholesterol was measured by Merck Kit while serum TG was measured using triglyceride reagent kit. No.5.17511.0001

Statistical Analysis: The data were analyzed in SPSS version 20. Difference in mean among the treatment groups was calculated by independent sample's test' for 2 groups comparison. One-way ANOVA test also was applied. $p \leq 0.05$ was considered significant.

RESULTS

A total of 15 mice were included in each group. Comparison of means values of body weight were compared for pre diabetic period, after HFD and at the end of experimentation. One-way ANOVA test (Table 1) was applied for comparison which resulted in insignificant values ($p=0.320$).

Table 2 shows the comparison of means with SD of all parameters including fasting blood glucose, serum adiponectin, serum resistin, serum triglyceride and serum cholesterol among both groups at the end of study. Serum cholesterol levels were 102.09 ± 3.71 mg/dl. Fasting blood glucose levels in group II were 147.46 ± 5.02 mg/dl. Serum adiponectin levels were 18.14 ± 0.46 ng/ml. Serum resistin levels were 2.94 ± 0.03 ng/ml. Serum triglycerides levels were 61.52 ± 2.78 mg/dl. Serum cholesterol levels were 72.93 ± 2.90 mg/dl. Statistically significant difference ($p < 0.001$) of fasting blood glucose, adiponectin, resistin, serum triglycerides and serum cholesterol were seen in group II, (pioglitazone) as compared to control group I, (NSS).

DISCUSSION

The invention of thiazolidinedione drugs was thought to play a crucial role in whole body metabolic homeostasis. But soon after their use in human beings, their side effects

Table 1: Comparison of weight of mice before experimentation, after HFD and at end of experimentation.

Group	n	Weight before experimentation	Weight after 1 st phase (HFD for 8 weeks)	Weight after one week of STZ injection	Weight at end of experimentation	p-value
I	15	27.39±0.8	37.59±1.0	36.66±1.34	28.56±0.7	0.320
II	15	26.90±0.8	36.87±1.0	36.62±1.23	29.92±1.4	

(excessive weight gain, bone loss, fluid retention, increased risk of heart failure and bladder carcinoma) raised questions for their use in clinical practice.¹⁵

Nigella sativa has been found to be effective as an additional therapy in patients of insulin resistance syndrome and it has a significant activity in diabetic and dyslipidemic patients.¹⁶ It decreases blood glucose levels by multiple mechanisms including decreased gluconeogenesis and glycogenolysis. It increases glucose uptake in liver, muscle and fat cells and improves antioxidant status in inflammatory conditions and has been investigated for proliferation of beta cells of pancreas in STZ induced diabetic mice.¹⁷

Matira et al, studied 60 adult male rats of the Long Evans strain (weighting about 200-250 g) and blood glucose levels in their control group were determined 5.32 mmol/lit.¹⁸ In another study by Abbas et al 40 healthy male albino mice weighing 25-40 gm were used; their fasting blood glucose levels were 106.25±1.51, which are also high from our control group possibly the mice weigh more than ours, and could be due to different chemical method used for estimation of fasting blood glucose.¹⁹

Anderson et al used two different strains of mice, Swiss Webster and C57 mice for their study and gave them HFD for 33 weeks, plasma adiponectin levels of control group were calculated 17ug/ml in Swiss Webster mice and 13ug/ml in C57 mice. Our results are similar, possibly because weights are same and they also have calculated total adiponectin levels and by Elisa method.²⁰ In our study, NSEE 250 mg/kg single daily dose by gavage treatment for 16 weeks resulted in amelioration of hyperglycemia in diabetic mice but pioglitazone did same statistically significantly better. Assaduzaman et al, showed similar results in their study. NSEE at dose of 300mg/kg, administered for 28 days to diabetic rats showed significant reduction of blood glucose levels, which was near glipalamide administration ($p<0.001$).²¹ Our study was different in aspect that we used pioglitazone instead of glipalamide.

In another study by Sultan et al, three groups of rats received Nigella sativa fixed oil (NSFO) and essential oil (NSEO) and one was diabetic control group. After 56 days, the groups receiving NSFO and NSEO resulted in enhanced insulin secretions as compared to substantial decrease in diabetic group. Total antioxidant capacity increased and malondialdehyde levels were decreased in Nigella treated groups. These results suggested that the mechanisms behind hypoglycemic potential of Nigella

Table 2: Difference in mean values of blood glucose, adiponectn, resistin, triglycerides and cholesterol at the end of study.

Groups Parameters	Group I (Nigella sativa) Mean ± SD	Group II (Pioglitazone) Mean ± SD	P- value
Blood glucose	189.20 ± 8.12mg/dl	147.46 ± 5.02mg/dl	<0.001
Adiponectin	16.98 ± 0.85 ng/ml	18.14 ± 0.46 ng/ml	<0.001
Resistin	2.88 ± 0.19 ng/ml	2.94 ± 0.03ng/ml	<0.001
Triglycerides	80.83 ± 3.67	61.52 ± 2.78	<0.001
Cholesterol	102.09 ± 3.71	72.93 ± 2.90	<0.001

sativa include increased insulin secretion and decreased oxidative stress in STZ induced diabetic rats.²² Pioglitazone used in our study is a known antidiabetic medication therefore it may have masked the effects of nigella in statistical analysis. Trials of nigella with placebo may be useful to cover this aspect.

Kanda et al, have also confirmed that adiponectin levels are increased with pioglitazone treatment. They used two different genetic mutated species for their study, six weeks old male (db/db) mice and (m/m) mice. Both species of mice were divided into two groups, treatment and control groups. The treatment groups received pioglitazone 30 mg/kg and the control group was administered vehicle. Blood was collected from the tail vein at 10 and 12 wk of age before and after intervention. The concentration of plasma adiponectin concentration was measured using the mouse adiponectin ELISA kit. Adiponectn levels increased to 70μg/ml from 40μg/ml in (m/m) mice and 55μg/ml from 25μg/ml in db/db mice.²³ Our study had similar results and pioglitazone was statistically significantly better in managing adiponectin levels as compared to Nigella. In a study by using a reporter gene assay, it was observed that NSEE behaves like an agonist of PPAR, while this effect was relatively small compared to that of rosiglitazone, but it was very important finding that suggests another possible and important mechanism by which Nigella Sativa ameliorates hyperglycemia and hyperlipidemia. Similar results were shown in our study as pioglitazone was better but still the impact of use of Nigella on various perimeters could not be negated.

A study by Moustafa et al,²⁴ compared Nigella Sativa and metformin for glycemic control and other parameters in patients suffering from diabetes mellitus. They concluded that NS administration in newly diagnosed T2DM was tolerable with no side effects as compared to metformin; however, it was inferior to metformin in terms of diabetes management. Our results are similar in the aspect that NS was inferior to a known glycemic agent used in our study,

pioglitazone. We recommend further studies in this regard and develop local guidelines regarding use of pioglitazone and other drugs of this group in patients suffering from type-II DM.

There were few limitations in our study. Histopathological changes in pancreas were not studied due to time and budget constraints. Moreover, Serum insulin levels were not done due to limited budget.

CONCLUSION

Pioglitazone significantly improved hyperglycemia, dyslipidemia, adiponectin and resistin in high fat diet, STZ induced diabetic mice in comparison to nigella sativa ethanolic extraction.

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REFERENCES

- Inoue Y, Qin B, Poti J, Sokol R, Gordon-Larsen P. Epidemiology of Obesity in Adults: Latest Trends. *Curr Obes Rep* 2018;7:276-88.
- Smitka K, Marešová D. Adipose tissue as an endocrine organ: an update on pro-inflammatory and anti-inflammatory microenvironment. *Prague Med Rep* 2015;116:87-111.
- Jung UJ, Choi MS. Obesity and its metabolic complications: the role of adipokines and the relationship between obesity, inflammation, insulin resistance, dyslipidemia and nonalcoholic fatty liver disease. *Int J Molecu Sci* 2014;11;15:6184-223.
- Esser N, Legrand-Poels S, Piette J, Scheen AJ, Paquot N. Inflammation as a link between obesity, metabolic syndrome, and type 2 diabetes. *Diab Res Clin Pract* 2014;31;105:141-50.
- Banerjee RR, Lazar MA. Resistin: molecular history and prognosis. *J Molecu Med* 2003;81:218-26.
- Berger JP, Akiyama TE, Meinke PT. PPARs: therapeutic targets for metabolic disease. *Trend Pharm Sci* 2005;26:244-51.
- Ferré P. The biology of peroxisome proliferator-activated receptors: relationship with lipid metabolism and insulin sensitivity. *Diabetes* 2004;53:S43-50.
- Ahmad A, Husain A, Mujeeb M, Khan SA, Najmi AK, Siddique NA, et al. A review on therapeutic potential of *Nigella sativa*: A miracle herb. *Asian Pacif J Trop Biomed* 2013;3:337-52.
- Najmi A, Nasiruddin M, Khan RA, Haque SF. Effect of *Nigella sativa* oil on various clinical and biochemical parameters of insulin resistance syndrome. *Int J Diabetes Dev Ctries* 2008;28:11.
- Benhaddou-Andaloussi A, Martineau L, Vuong T, Meddah B, Madiraju P, Settaf A, et al. The in vivo antidiabetic activity of *Nigella sativa* is mediated through activation of the AMPK pathway and increased muscle Glut4 content. *Evidence-Based Compl Altern Med* 2011;1-11.
- Dawane JS, Pandit VA, Bhosale MS, Khatavkar PS. Evaluation of Effect of Nisha Malaki on STZ and HFHF Diet Induced Diabetic Neuropathy in Wistar Rats. *J Clin Diagnostic Res* 2016;10:FF01.
- Obrosova A, Shevalye H, Coppey LJ, Yorek MA. Effect of tempol on peripheral neuropathy in diet-induced obese and high-fat fed/low-dose streptozotocin-treated C57Bl6/J mice. *Free Rad Res* 2017;51:360-7.
- Dong HY, Jiang XM, Niu CB, Du L, Feng JY, Jia FY. Cerebrospinal improves sciatic nerve dysfunction in a mouse model of diabetic peripheral neuropathy. *Neural Regen Res* 2016;11(1):156-9.
- Balbua M, El-Zeftawy M, Ghareeb D, Taha N, Mandour AW. *Nigella sativa* relieves the altered insulin receptor signaling in streptozotocin-induced diabetic rats fed with a high-fat diet. *Oxid Med Cell Longev* 2016;1-16.
- Wang QA, Zhang F, Jiang L, Ye R, An Y, Shao M, et al. Peroxisome proliferator-activated receptor γ and its role in adipocyte homeostasis and thiazolidinedione-mediated insulin sensitization. *Mol Cell Biol* 2018;38:e00677-17.
- Yagi SM, Yagi AI. Traditional medicinal plants used for the treatment of diabetes in the Sudan: A review. *Afr J Pharm Pharmacol* 2018;12:27-40.
- Kanter M, Meral I, Yener Z, Ozbek H, Demir H. Partial regeneration/proliferation of the β -cells in the Islets of Langerhans by *Nigella sativa* L. in streptozotocin-induced diabetic rats. *Tohoku J Exp Med* 2003;201:213-9.
- Khanam M, Dewan ZF. Effects of the crude and the n-hexane extract of *Nigella sativa* Linn. (kalajira) upon diabetic rats. *Bangladesh J Pharm* 2008;4:17-20.I
- Abbas AH. Antihyperglycemic, antihyperlipidemic effects of ethanol extract of *nigella sativa* seeds in streptozotocin/high fat diet induced hyperglycemic mice. *World J Pharmacy Pharmaceut Sci* 2018;7:85-117.
- Anderson NJ, King MR, Delbruck L, Jolivald CG. Role of insulin impairment, adiponectin, and dyslipidemia in peripheral and central neuropathy in mice. *Dis Models Mechan* 2014;015750.
- Asaduzzaman M, Nahar L, Hasan M, Khatun A, Shajedul Haque M. Antihyperglycemic Activity, Antihyperlipidemic Activity, Hepatoprotective Activity and Histopathological Analysis of Natural Honey in Streptozotocin Induced Diabetic Rats. *J Cytol Histol* 2016;7:402
- Sultan MT, Butt MS, Karim R, Zia-Ul-Haq M, Batool R,

- Ahmad S, et al. Nigella sativa fixed and essential oil supplementation modulates hyperglycemia and allied complications in streptozotocin-induced diabetes mellitus. Evidence-Based Compl Alter Med 2014;1-8.
23. Kanda Y, Shimoda M, Hamamoto S, Tawaramoto K, Kawasaki F, Hashiramoto M, et al. Molecular mechanism by which pioglitazone preserves pancreatic β -cells in obese diabetic mice: evidence for acute and chronic actions as a PPAR γ agonist. Am J Physiol Endocrinol Metabol 2009;298:E278-86.
24. Moustafa HAM, El Wakeel LM, Halawa MR, Sabri NA, El-Bahy AZ, Singab AN. Effect of Nigella Sativa oil versus metformin on glycemic control and biochemical parameters of newly diagnosed type 2 diabetes mellitus patients. Endocrine 2019;65:286-94.

In vitro insights: Investigating Pro-apoptotic potential of capsaicin against HL-60, Human Leukemia cell line

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Objective: To investigate the pro-apoptotic potential of capsaicin on Human Leukemia HL-60 cell line as a potent natural chemotherapeutic agent.

Methodology: This study was conducted at Forman Christian College, Lahore from January to April-2024. It included culturing HL-60 cell line and its treatment with serial concentrations of capsaicin for calculation of subsequent IC50 values via MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide] assay, expression analysis of gene, comparative analysis of relative gene fold (Intrinsic Biomarkers Caspase-3, Caspase-9) as apoptosis mediator markers followed by RT-qPCR. Cellular apoptotic morphology was confirmed via Hoechst 333258 staining.

Results: For HL-60 cell line, the IC50 of capsaicin (16.7uM) showed high gene expression of pro-apoptotic biomarkers (Caspase-3 and Caspase-9). Hoechst 333258 staining showed prominent apoptotic bodies leading to nuclear fragmentations.

Conclusion: Capsaicin had robust pro-apoptotic potential leading to diagnostic efficacy against leukemia HL-60 cell line. Further studies would help in identifying key mechanisms by which capsaicin exhibits anti-apoptotic potential against HL-60 cell lines.

Keywords: Capsaicin, pro-apoptotic effects, anti-cancer mechanisms, HL-60, natural chemotherapeutics.

INTRODUCTION

Leukemia is a form of blood cancer. In context of advanced chemotherapeutic regimens causing poor prognoses, patients tend to face short- and long-term adverse effects of anti-cancer agents. The natural sources may reduce the shortcomings of cancer drugs. The last three decades have been very important in targeting anti-cancer potential of dietary phytoconstituents.

Capsaicin is concentrated in the seeds and white pith of chili peppers (*Capsicum annum*) and plays role as a potent inducer of apoptosis having a long history of medicinal use for the treatment of diabetes, asthma, arthritis, gastrointestinal complications and even for cancer.¹ Being Phytochemical, capsaicin vastly modulates cellular signaling pathways crucial for cancer development, induces DNA damage, influences DNA repair mechanisms and consequently a disruptor of cancer cells metabolism through molecular warfare.² Due to multidirectional potential both compounds have long been used in medicine and pharmacology.³ Antitumor activity has been reported for several tumors cell lines and capsaicin has a high apoptotic potential.⁴

HL-60 is leukemia cell lines having adherent growth properties. Capsaicin has apoptosis-inducing chemotactic properties in HL-60 cells dependent on Reactive Oxygen Species and influencing signal pathways and killing cancer cells.⁵ Phytochemicals possess potent bioactive

anti-cancer activity against HeLa cell lines showing cell cycle arrest and reduced angiogenesis when combined to cisplatin.^{6,7} Cisplatin is designated with pre-defined MTT (3-[4,5-dimethylthiazol-2-yl]-2,5 diphenyl tetrazolium bromide) assay values and therefore it is used as a standard to check the anti-cancer and anti-growth properties of selected constituent of phytochemical. This study highlighted the pro-apoptotic effects of Eugenol and its orthodimer called Bis-Eugenol on the Human Leukemia HL-60 cell line by distinguishing it as a potent natural anti-cancer agent having greater efficacy and good prognosis with low chemical doses.

METHODOLOGY

This inter-collaborative study was conducted in the cell culture Laboratories of Forman Christian College (A Chartered University) Lahore and Liaquat University of Medical and Health Sciences from January to April-2024, after Ethical Review Committee of Foreman Christian College (Ref: ERC-143/01/01/2024).

Capsaicin was extracted from the powdered seeds and white pith of chili peppers (*Capsicum annum*). As per the experimental scheme of this study (Fig. 1), the first step was extraction of capsaicin. Briefly, collected phyto-components were converted into the fine powder by grinding them under hygiene conditions followed by freeze drying at -55°C using a freeze dryer (Alpha 1-2 LD

plus D-37520, CHRIST Germany). Then crushed using a mortar and pestle under extreme care to avoid contamination. Powder formation increases the surface area that facilitates the extraction process in ethanol solvent undergoing maceration (reflux extraction) until maximized yield.

Dulbecco's Modified Eagle Medium For treatment of cells, customized concentrations of 10, 20, 40 and 60 ($\mu\text{g/ml}$) were freshly prepared Gibco (Dulbecco's Modified Eagle Medium) DMEM (catalog#11966025) medium supplemented (or enriched) with L-glutamine (2mM), 10% fetal bovine serum (FBS), sodium pyruvate (1%), penicillin and streptomycin (100 IU/mL) and vortex for 10-12 minutes.

HL-60 cells were initially obtained from cell culture Laboratory of University of Lahore, extracted from leukemic blood samples, and stored in pre-defined Cryo vials preparations in Liquid Nitrogen at -180°C . After thawing and following routine sub culturing protocols, cells were cultured in supplemented Medium (10% Fetal Bovine Serum) and treated with pre-formulated concentrations of capsaicin (05, 10, 15, 20, 25, and 30 μM) for MTT assays of 24, 48, and 72 hours, respectively.

Cells (10000 cells/well) were seeded in 96-well plates (100 μL media/well), at pre-optimized cell densities and were treated with serial dilutions of increasing concentrations (10, 20, 40 and 60 $\mu\text{g/ml}$) of four compounds and their combinations for incubation period of 24, 48, and 72 hours, respectively to find out IC₅₀ values. 96-well plates were designed in a way that the triplicate of wells undergoing same treatment concentrations and reading of MTT assay at 480nm were recorded and average of readings were taken to minimize the chances of random and systematic errors. After the treatment, MTT solution (10 mg/mL in PBS) was added

at a volume of 10 μL /well and the plate was incubated for 4 hours at 37°C and 5% CO_2 .

After reproducing the experiments, as per greater reproducibility only 24hours MTT was selected for IC₅₀, the concentration at which approximately 50% cells were found dead). From treated cells, total RNA extraction was performed followed by Quality check ($\text{ng}/\mu\text{L}$) and cDNA synthesis as per Kit Protocols (Reagent Catalog# AM7832, Thermofisher Scientific, USA). Primers sets of Caspase-3 and Caspase-9 are shown in Table 1. Primers were designed on serial cloner by taking the consensus CDS sequence of required genes from NCBI and confirmed by doing In-Silico PCR on UCSC Genome Browser. Gradient PCR reactions were done multiple times to achieve optimization.

To stain the nucleus, Hoechst 33258 was used producing blue florescence. HL-60 cells were incubated after treatment with IC₅₀ of Capsaicin treated cells. After removing culture media, the cell smear (first dried) immersed in the prepared concentration of formaldehyde upto 4%. Then after soaking with PBS, washed the smear three times and fully covered with Hoechst 33258 (solution). After keeping it at room temperature for 15 minutes, PBS was used for washing (two to three repetitions). It was sealed to observe under microscope.

Statistical Analysis: Data were analyzed using SPSS version 26.

RESULTS

HL-60 cells were treated with serial concentrations of capsaicin (5, 10, 15, 20, 25 and 30 μM) and MTT assay was performed to calculate the IC₅₀ values. Out of 24-, 48- and 72-hours assays, due to higher experimental reproducibility of MTT assay values only 24 hours MTT assay was selected to proceed further by concluding best IC₅₀ of Capsaicin (IC₅₀ of 11.9 μM) treatments were

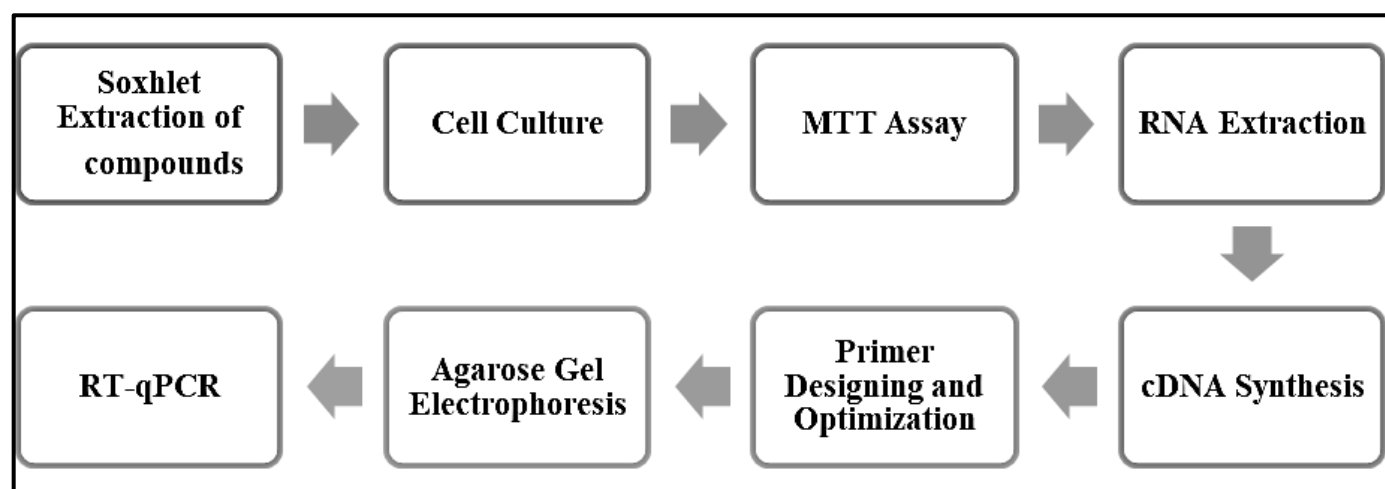


Fig. 1: Schematic representation of the experimental plan.

performed in comparison with cisplatin (control). Gene expression profiling (Caspase 3 and Caspase 8) was performed to analyze the pro-apoptotic. Significant associations with the higher relative gene fold depict the efficacy of compounds on HL-60 cells as shown in Fig. 2.

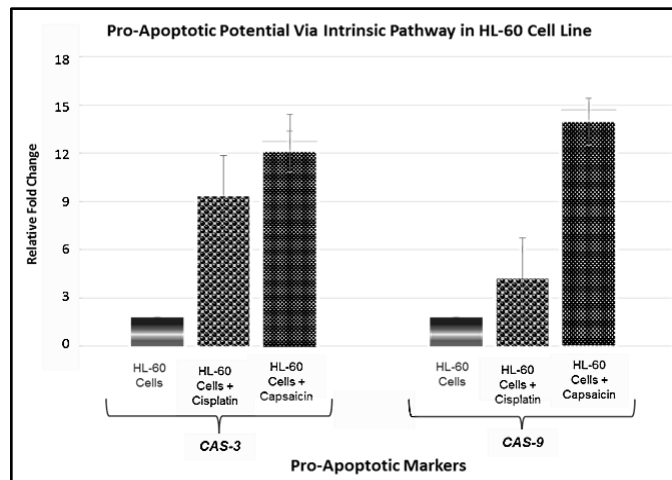


Fig. 2: MTT Assay (Expression Profiling of Selected Biomarkers).

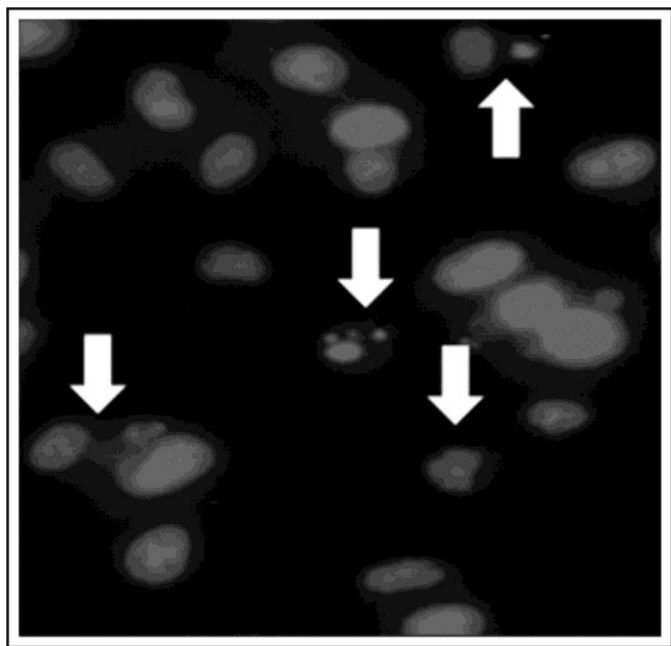


Fig. 3: Apoptotic morphology of HL-60 cells line (HOECHST 33258 staining).

Both Biomarkers (Caspase-3 and Caspase-9) showed significant expressions as compared to control cells and capsaicin treatment. Overall Relative Gene fold of Caspase-9 (14.1) was found higher as compared to Caspase-3 (12.0). Apoptotic morphology of HL-60 cells line is shown in Fig. 3.

Table 1: Sequences of Caspase-3 and Caspase-9 Primers set.

BIOMARKER GENES	SEQUENCES OF SELECTED PRIMERS
Caspase-3	Forward: 5'GCGAATCAATGGACTCTGG3'
	Reverse: 5'GACATCTGTACCAGACCGAG3'
Caspase-9	Forward: 5'CAGGCCCATATGATCGAG3'
	Reverse: 5'CTGTGTCCTCTAAGCAGGAGA3'

DISCUSSION

Capsaicin has the ability to interfere with the initiation and promotion of cancer, has demonstrated anti-oxidative, anti-inflammatory, pro-apoptotic, anti-proliferative, and anti-tumorigenic activities in multiple cancer cell lines.⁸ Similar to many previous studies, results obtained from our study showed that treatment of HL-60 cells with capsaicin led to a greater induction of expression of Caspase-3 and Caspase-9 confirming pro-apoptotic (intrinsic) potential of compounds as a major contributing factor to the decrease in cell proliferation.^{9,10} Similar results were obtained where piperine induced the expression and subsequent activity of both Caspase-3 and Caspase-8 leading to the apoptosis of the HeLa, human cervical cancer, cells.¹¹ A group of researchers suggested that capsaicin with very low doses (08μM) interfered with the process of carcinogenesis by inhibiting Breast cancer cells %age and inhibiting the activity of MMP (matrix metalloproteinase).^{12,13}

Flow cytometrical analysis on Leukemia cell lines after treating with IC₅₀ of cinnamaldehyde and Thymoquinone showed similar congestions in cell size and altered granularity.¹⁴ Another experiment on HepG2 cell lines showed decrease in size and varied granularity as indicated by many studies on the effect of Capsaicin on Cancer cell lines.¹⁵ Our findings were that capsaicin possess strong membrane permeability potential to rupture cell membranes and destroy the cellular metabolic machinery in experiments of in vitro analysis.¹⁶

A study suggested that after phytochemical extract treatments, many apoptotic bodies along with disrupted cells showing nuclear fragmentations were seen under florescence microscope with Hoechst 33258 Stain.¹⁷ The addition of Eugenol is believed to enhance the inhibition of breast cancer stem cells by cisplatin by inhibiting the activity of aldehyde dehydrogenases (ALDH) and ALDH positive tumor initiating cells and enhancing NF-κB signaling pathway inhibition.¹⁸ On the whole both compounds showed significant pro-apoptotic potential. In the future, the synergistic effect of both capsaicin with other natural phytochemicals should be studied on

multiple other cell lines to understand how these compounds work and if their affectivity is altered.

CONCLUSION

Our findings supported the evidence of pro-apoptotic potential of capsaicin on the HL-60 cells. It was also noted that the capsaicin showed strong chemoprotective potential. The mechanism of action of these compounds, in combination, needs to be studied better *in vivo*.

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REFERENCES

- Alabi BA, Aderonmu A, Lawal SK, Nku-Ekpang O-AT, Ajayi M, Iwalewa OE. Evaluation of the modulatory effects of Capsicum chinensis methanol extract in streptozotocin-induced diabetic neuropathic pain in mice. *Tanz J Sci* 2023;49:930-42.
- Talib WH, AlHur MJ, Al. Naimat S, Ahmad RE, Al-Yasari AH, et al. Anticancer effect of spices used in Mediterranean diet: preventive and therapeutic potentials. *Front Nutr* 2022;9:905658.
- Basith S, Cui M, Hong S, Choi SJ. Harnessing the therapeutic potential of capsaicin and its analogues in pain and other diseases. *Molecules* 2016;21;8:966.
- Kujumgiev I. Activation of the tumor-inducing ability of *Agrobacterium tumefaciens* (Smith and Townsend) Conn. by means of capsaicin. *Arch Microbiol* 1968;62:284-8.
- Shotorbani NY, Jamei R, Heidari R. Antioxidant activities of two sweet pepper *Capsicum annuum* L. varieties phenolic extracts and the effects of thermal treatment. *Avic J Phytomed* 2013;3(1):25-34.
- Damodaran B, Nagaraja P, Jain V, Wimalasiri MMV, Sankolli G, Kumar G, et al. Phytochemical screening and evaluation of cytotoxic activity of *Calotropis gigantea* leaf extract on MCF7, HeLa, and A549 cancer cell lines. *J Nat Sci Biol Med* 2019;10:131-8.
- Aziz O, Suleman A, Fatima Z, Yasin A, Nasir A, Ubaid M, et al. Eugenol's molecular warfare against human leukemia K562 cells: in vitro insights to chemotherapeutic potentials. *J Health Rehabil Res* 2024;4:943-9.
- Oyagbemi A, Saba A, Azeez O. Capsaicin: a novel chemo preventive molecule and its underlying molecular mechanisms of action. *Int J Cancer* 2010;47:53-8.
- Wang Y, Ma W, Zheng W. Deguelin, a novel anti-tumorigenic agent targeting apoptosis, cell cycle arrest and anti-angiogenesis for cancer chemoprevention. *Mol Clin Oncol* 2013;1:215-9.
- Liu T, Wang G, Tao H, Yang Z, Wang Y, Meng Z, et al. Capsaicin mediates caspases activation and induces apoptosis through P38 and JNK MAPK pathways in human renal carcinoma. *BMC Cancer J* 2016;16:1-13.
- DiazVidal T, Armenta-Pérez VP, Rosales-Rivera LC, Basulto-Padilla GC, Martínez-Pérez RB, Mateos-Díaz JC et al. Long chain capsaicin analogues synthesized by CALB-CLEAs show cytotoxicity on glioblastoma cell lines. *Applied Microbiology and Biotechnology*. 2024;108:1-4.
- Ying TH, Yang SF, Tsai SJ, Hsieh SC, Huang YC, Bau DT, et al. Fisetin induces apoptosis in human cervical cancer HeLa cells through ERK1/2-mediated activation of caspase-8/-caspase-3-dependent pathway. *Arch Toxicol* 2012;86:263-73.
- Cherifi F, Rousselle J-C, Namane A, Laraba-Djebari F. Use of nano-liquid chromatography and mass spectrometry to identify a new *Cerastes* venom phospholipase *Adv Nanot* 2010;30:99-100.
- Lee GR, Jang SH, Kim CJ, Kim AR, Yoon DJ, Park N-H, et al. Capsaicin suppresses the migration of cholangiocarcinoma cells by down-regulating matrix metalloproteinase-9 expression via the AMPK–NF-κB signaling pathway. *Clin Exp Metast* 2014;31:897-907.
- Sadeghi S, Davoodvandi A, Pourhanifeh MH, Sharifi N, ArefNezhad R, Sahebnaasagh R, et al. Anti-cancer effects of cinnamon: Insights into its apoptosis effects. *European journal of medicinal chemistry* 2019;178:131–140.
- Dai N, Ye R, He Q, Guo P, Chen H, Zhang Q. Capsaicin and sorafenib combination treatment exerts synergistic anti-hepatocellular carcinoma activity by suppressing EGFR and PI3K/Akt/mTOR signaling. *Oncology Reports*. 2018;40:3235-48.
- Islam SS, Al-Sharif I, Sultan A, Al-Mazrou A, Remmal A, Aboussekhra A. Eugenol potentiates cisplatin anti-cancer activity through inhibition of ALDH-positive breast cancer stem cells and the NF-κB signaling pathway. *Mol Carcinogens* 2018;57:333-46.

Investigating Hesperidin as a potential neuroprotective agent for Autism-induced Rats Models

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Objective: To explore the neuroprotective potential of hesperidin in rats that have been exposed to propionic acid-induced autism and correlation assessment analysis with serum *BDNF* levels, a biomarker for neuroprotection.

Methodology: The study included 25 healthy male 7 weeks-old Sprague-Dawley rats and five groups were designed. Group I included physiological rats (n=5) that were not induced, while the other groups (n=20) received intraperitoneal injections of propionic acid (250 mg/kg/day) for 5 days. Group II was exclusively made up of rats that had been induced with PPA. Groups III, IV, and V involved the rats that were given different dosages of hesperidin (100 mg/kg, 200 mg/kg, and 400 mg/kg, respectively) mixed into their diet for a 24-day period. Hesperidin effects were assessed by measuring *BDNF* levels via ELISA kits. One-way ANOVA (post hoc Tukeys test) were used in statistical analysis.

Results: Significant recovery of serum *BDNF* levels was seen in the Hesperidin treated groups (III, IV and V) relative to the PPA-induced group (II). Hesperidin therapy greatly reduced autism-like problems. The measured *BDNF* levels (ng/ml) were as Group I (15.2±0.5), II (6.8±0.4), III (10.3±0.5), IV (13.0±0.6) and V (14.7±0.5). Significant differences between the groups were found using a one-way ANOVA (p<0.001). *BDNF* levels in Groups III, IV, and V were considerably greater than those in Group II (PPA-induced), according to the post-hoc Tukeys test (p<0.05).

Conclusion: Increased *BDNF* levels in a mouse model of PPA-induced autism supported the neuroprotective effects of hesperidin.

Key Words: *BDNF*, Autism-induced Models, propionic acid, neurodegeneration, autism, hesperidin.

INTRODUCTION

Autism disorders (ASD) is defined by notable discrepancies in social dealings, appearance before 30 months of age, gross distortions or deficits in language development, and peculiar, sometimes rigid attachments to objects, and the manifestation of monotonous behaviors. ASD has multifaceted etiology that includes neurological, environmental, and genetic components. One of the environmental variables linked to the emergence of ASD-like behavior is exposure to certain chemicals and medicines during crucial developmental stages.¹

In animal models, propionic acid (PPA), a short chain fatty acid which is frequently produced as a byproduct of gut microbial metabolism has been utilized to elicit behaviors similar to those of ASD. Administering PPA to rats causes behavioral problems, oxidative stress, neuroinflammation, and changes in neurotransmitter systems. This is useful for looking into possible treatments that could lessen the neurobehavioral and neurodevelopmental impacts of autism.²

Citrus fruits including oranges, lemons, and grapefruit contain the bioflavonoid hesperidin, which has drawn interest due to its wide variety of pharmacological characteristics. Its neuroprotective, anti-inflammatory, and antioxidant properties are well established.³ The capacity of hesperidin to control several signaling pathways, lower oxidative stress, and inhibit neuroinflammation has been linked to its neuroprotective effects. Hesperidin may have an impact on serum brain-derived neurotrophic factor (*BDNF*) levels, which are essential proteins related to neurodevelopment, synaptic plasticity, and cognitive functions, according to recent research.⁴

A vital protein in the neurological system, *BDNF* is essential for the survival, development, and maintenance of neurons.⁵ Its neuroprotective mechanism encompasses many critical mechanisms that are essential in the fight against neurodegeneration, especially in situations such as ASD. The main way that *BDNF* works is by attaching itself to the high-affinity receptor known as tropomyosin receptor kinase B, which sets off a series of intracellular

signaling cascades.⁶ These pathways, which support neuronal survival, differentiation, and synaptic plasticity, include the MAPK/ERK, P13K/Akt, and PLC γ pathways. Through improving synaptic strength and connectivity, BDNF works to mitigate the synaptic deficiencies and cognitive impairments linked to ASD.⁷ BDNF contributes to the modulation of synaptic plasticity, a critical mechanism for memory and learning. Strengthening synaptic connections is crucial for efficient brain transmission and cognitive function, and BDNF does this via promoting long-term depression.⁸ Oxidative stress and neuro-inflammation are common in neurodegenerative diseases and are regulated by BDNF.⁹ Moreover, neurogenesis-the process by which new neurons are created in the brain-is facilitated by BDNF. Enhancing neurogenesis can aid in replacing lost or injured neurons, repairing brain circuits and enhancing functional results. Hesperidin ameliorates anxiety-depressive-like behavior in 6-OHDA model of Parkinson's disease by regulating striatal cytokine and neurotropic factors levels and dopaminergic innervation loss in the striatum of mice.¹⁰ We aimed to explore the neuroprotective potential of hesperidin in rats that have been exposed to propionic acid-induced autism and correlation assessment analysis with serum BDNF levels, a biomarker for neuroprotection in ASD.

METHODOLOGY

After Research Ethical Committee approval (REC-785/12/07/2019), this inter-collaborative study was carried out in LUMHS, Animal House and Department of Anatomy Agriculture University, Jamshoro from July, 2019 to June, 2020. Male rats (n=25) in good health (7 weeks old) with an average weight (28–35 grams) were part of this study.

The experimental scheme of each of the five groups (n=5x5) was as follows: Group I: (Non-induced/regular rats) negative control group fed on a regular diet.

Group II: (Autism-induced) positive control group (no treatment) PPA treatment for 5 days. Group III: (Autism-induced) Treatment group 1(100mg/kg hesperidin for 25 days), Group IV: (Autism-induced) Treatment group 2 (200 mg/kg hesperidin for 25 days) and Group V: (Autism-induced) Treatment group (400mg/kg hesperidin for 25 days).

PPA 250 mg/kg/day in normal saline was given for five days to induce autism. After intra-peritoneal injection, rats were maintained under observation. BDNF levels were measured after giving rats various dosages of hesperidin for a whole day. BDNF levels were measured using ELISA kits (Catalogue#KE00096-Proteintech-Germany).

Statistical Analysis: Version 21 of SPSS was used to analyze the data. Post hoc testing and analysis of ANOVA was used to analyze the variables. $p < 0.05$ was considered significant.

RESULTS

Results are accumulative mean NC= Negative control, PC= Positive control, H1=100mg/kg of hesperidin, H2= 200mg/kg hesperidin, and H3=400mg/kg hesperidin. Mean values of BDNF levels statistically found with the non-significance of ($p < 0.05$) (Table 1).

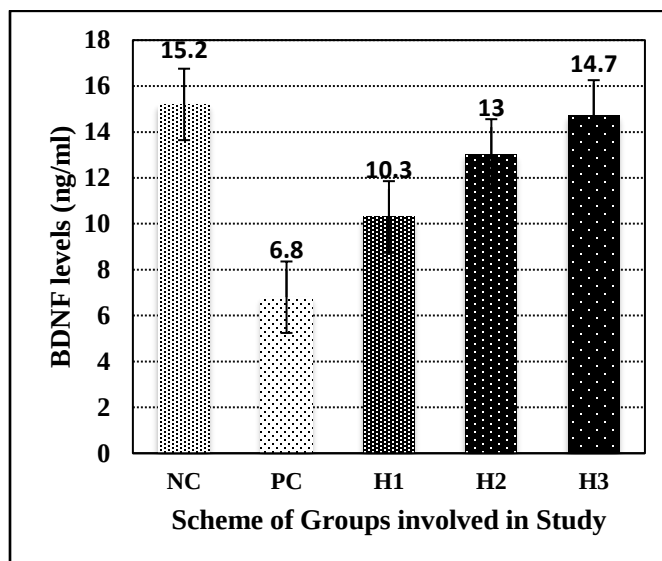


Fig. 1: Comparative analysis of BDNF levels in the experimental groups.

NC = negative control, PC= Positive control, H1= treatment group 1(100mg/kg), H2= Treatment group 2(200mg/kg) and H3= Treatment group 3 (400mg/kg).

Accumulative means of BDNF levels are presented in figure 2 and table 1. The neurodegenerative results of the positive control group (6.8) were highly significant in comparison to treatment groups. The BDNF levels increased in all the treatment groups as compared to the positive control group.

Accumulative means of BDNF levels are presented in figure2 and table 1. The results of BDNF levels (ng/ml) in positive control group II (6.8 ± 0.4) were highly significant in comparison to other treatment groups. Considering neurodegenerative recovery index in the treated rats (group III, IV and V) the BDNF levels were increased in all the treatment groups with the increase in hesperidin concentrations confirming the efficacy of Hesperidin as a neuro-protective agent. Mean values of BDNF levels statistically found with the non-significance of ($p < 0.05$) (Fig. 1). As paralleled to the positive control

Table 1: Accumulative mean values + standard error of *BDNF* levels (ng/ml).

Groups	I	II	III	IV	V	p-value
Parameters	NC	PC	HT1	H2	H3	
<i>BDNF</i> Levels (ng/ml)	15.2±0.5	6.8±0.4	10.3±0.5	13.0±0.6	14.7±0.5	0.05

group with the maximum recovery in group V *BDNF* levels ng/ml (14.7±0.5).

DISCUSSION

Flavonoids are one of the most numerous and thoroughly studied families of chemicals produced from medicinal plants with neuroprotective, anti-inflammatory, and antioxidant properties. A study used the valproic acid to induce the autism like symptoms in rodents and then they were treated with flavonoids, which showed neuroprotective properties helping to reduces the autism-like symptoms.¹¹

In a mice-based model of PPA was used to induce autism, the current work showed the substantial neuroprotective benefits of hesperidin doses. We found that hesperidin therapy significantly reduced the symptoms of autism-like illness by raising *BDNF* levels in treated groups relative to PPA-induced groups. A study by Abdollahi et al, reported that hesperidin with doses of 100 to 160mg/kg showed potent neuroprotective and oxidative properties and it induced the *BDNF* pathway leading to its regulation of production which proved to increase the *BDNF* levels upto 14.5 ng/ml.¹² Another study had similar results.¹³

A number of neuropsychiatric and neurodevelopmental illnesses, including ASD, had been linked to decreased *BDNF* levels.¹⁴ The neurotoxic effects of PPA were evident in our study, as evidenced by the significantly lower *BDNF* levels in the PPA-induced group.¹⁵ The maximum dosage of hesperidin (400 mg/kg) nearly restored *BDNF* levels in a dose-dependent manner, suggesting that hesperidin's neuroprotective effects might be regulated at least to some extent, by its ability to increase *BDNF* levels.¹⁶

The robustness of hesperidin's effects is shown by the substantial differences in *BDNF* levels across the groups as analyzed by using one-way ANOVA ($p < 0.05$) and further supported by the post hoc Tukeys test ($p < 0.05$). These statistical studies demonstrated the potential of hesperidin as an agent for managing ASD by considerably restoring *BDNF* levels.

Several recent studies had emphasized the role that *BDNF* plays in preserving neural health and function. According to group of researchers, substances that raised *BDNF* levels may be able to reduce the symptoms of neurodevelopmental diseases.^{17,18} Our research showed

similar results.

The anti-inflammatory and antioxidant characteristics of hesperidin may potentially be responsible for its neuroprotective benefits. It had been demonstrated that hesperidin lowers inflammation and oxidative stress, two important factors in the pathogenesis of ASD.^{19,20} This would increase the production of *BDNF* and improve neurobehavioral outcomes.^{21,22}

Future research should focus on elucidating the precise molecular mechanisms through which hesperidin enhances *BDNF* levels and long-term studies are necessary to investigate the sustained impact of Hesperidin in clinical trials to determine the safety, efficacy, and optimal dosage of hesperidin in human subjects with ASD. Additionally, exploring the potential synergistic effects of hesperidin in combination with other neuroprotective agents could provide more comprehensive treatment strategies for ASD.

CONCLUSION

Increased *BDNF* levels in a mouse model of PPA-induced autism supported the neuroprotective effects of dose-dependent response of hesperidin. Our findings highlighted the hesperidin's therapeutic potential in managing the ASD.

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REFERENCES

1. Al-Dewik N, Al-Jurf R, Styles M, Tahtamouni S, Alsharshani D, Alsharshani M, et al. Overview and introduction to autism spectrum disorder (ASD). *Autism Res Treatment* 2020;24:3-42.
2. Meeking MM, MacFabe DF, Mephram JR, Foley KA,

- Tichenoff LJ, Boon FH, et al. Propionic acid induced behavioural effects of relevance to autism spectrum disorder evaluated in the hole board test with rats. *Behav Brain Res* 2020;97:109794.
3. Scoditti E. Neuroinflammation and neurodegeneration: The promising protective role of the citrus flavanone hesperetin. *Nutrients* 2020;12:2336.
 4. Li X, Huang W, Tan R, Xu C, Chen X, Li S, et al. The benefits of hesperidin in central nervous system disorders, based on the neuroprotective effect. *Biomed Pharmacotherapy* 2023;159:114222.
 5. Yurtal Z, Altuğ EM, Unsaldı E, Secimci El, Kucukgul A. Investigation of neuroprotective and therapeutic effects of hesperidin in experimental spinal cord injury. *Neurosci Letters* 2020;715:134631.
 6. Cappoli N, Tabolacci E, Aceto P, Russo D. The emerging role of the BDNF-TrkB signaling pathway in the modulation of pain perception. *J Neurosci Res* 2020;98:1436-1449.
 7. Abdelli LS, Samsam A, Naser SA. Propionic acid induces gliosis and neuro-inflammation through modulation of PTEN/AKT pathway in autism spectrum disorder. *Scientific Rep* 2019;9:8824.
 8. Ibrahim AM, Chauhan L, Bhardwaj A, Sharma A, Fayaz F, Kumar B, et al. Brain-derived neurotrophic factor in neurodegenerative disorders. *Front Neurosci* 2022;10:1143-7.
 9. Liu X, Lin J, Zhang H, Khan NU, Zhang J, Tang X, et al. Oxidative stress in autism spectrum disorder—current progress of mechanisms and biomarkers. *Front Psychiatry* 2022;13:813304-7.
 10. Antunes MS, Cattelan Souza L, Ladd FVL, Ladd AABL, Moreira AL, Bortolotto VC, et al. Hesperidin ameliorates anxiety-depressive-like behavior in 6-OHDA model of Parkinson's disease by regulating striatal cytokine and neurotrophic factors levels and dopaminergic innervation loss in the striatum of mice. *Behav Brain Res* 2020;57:3027-41.
 11. Amini F, Amini-Khoei H, Haratizadeh S, Setayesh M, Basiri M, Raeiszadeh M, et al. Hydroalcoholic extract of *Passiflora incarnata* improves the autistic-like behavior and neuronal damage in a valproic acid-induced rat model of autism. *Molecular Neurobiol* 2023;60:315-24.
 12. Abdollahi H, Edalatmanesh MA, Hosseini E, Foroozanfar M. The effects of hesperidin on BDNF/TrkB signaling pathway and oxidative stress parameters in the cerebral cortex of the utero-placental insufficiency fetal rat model. *Brain Res Bull* 2021;174:73-81.
 13. Alhusaini A, Hasan IH, Alrumayyan B, Alesikri M, Alanazi K, Almasoud R, et al. Neuroprotective efficacy of nano-CoQ against propionic acid toxicity in rats: Role of BDNF and CREB protein expressions. *J Biochem Molecular Toxicol* 2020;34:22449-53.
 14. Saad AK, Akour A, Mahboob A, AbuRuz S. Role of brain modulators in neurodevelopment: focus on autism spectrum disorder and associated comorbidities. *J Pediatr Neurol* 2022;15:612-23.
 15. Alsubaiei SRM, Alfawaz HA, Bhat RS, El-Ansary A. Nutritional intervention as a complementary neuroprotective approach against propionic acid-induced neurotoxicity and associated biochemical autistic features in rat pups. *Nutrients* 2023;15:738-42.
 16. Barbosa AG, Pratesi R, Paz GSC, Dos Santos MAAL, Uenishi RH, Nakano EY, et al. Assessment of BDNF serum levels as a diagnostic marker in children with autism spectrum disorder. *Scientific Rep* 2020;10:17348.
 17. Cichon N, Saluk-Bijak J, Gorniak L, Przyslo L, Bijak M. Flavonoids as a natural enhancer of neuroplasticity—An overview of the mechanism of neurorestorative action. *Nutrients* 2020;12:1035-9.
 18. Guazelli CF, Fattori V, Ferraz CR, Borghi SM, Casagrande R, Baracat MM, et al. Antioxidant and anti-inflammatory effects of hesperidin methyl chalcone in experimental ulcerative colitis. *Chemico-Biol Interactions* 2021;333:109315.
 19. Sharma P, Kumari S, Sharma J, Purohit R, Singh D. Hesperidin interacts with CREB-BDNF signaling pathway to suppress pentylenetetrazole-induced convulsions in zebrafish. *Front Pharmacol* 2021;11:607797.
 20. Hajjalyani M, Hosein Farzaei M, Echeverría J, Nabavi SM, Uriarte E, Sobarzo-Sánchez E. Hesperidin as a neuroprotective agent: a review of animal and clinical evidence. *Molecules* 2019;24:648-52.
 21. Joshi S, Dhingra AK, Chopra B, Guarve K, Bhateja D. Therapeutic potential and clinical evidence of hesperidin as neuroprotective agent. *Central Nervous Sys Agents Medicinal Chem* 2022;22:5-14.
 22. Li X, Huang W, Tan R, Xu C, Chen X, Li S, et al. The benefits of hesperidin in central nervous system disorders, based on the neuroprotective effect. *Biomed Pharmacotherapy* 2023;159:114222.

Prevention of doxorubicin-associated cardiac toxicity by metformin, vitamin E, and carvedilol: A comparative study

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Objective: To compare evading effects of alpha tocopherol, carvedilol, and metformin on early detection of myocardial damage caused by doxorubicin.

Methodology: This randomized in-vivo study in rabbits was performed from Oct 2021 to March 2022 at Department of Pharmacology & Therapeutics, Wah Medical College. A cohort of 30 healthy albino male adult rabbits were used. Cardiotoxicity was induced in one group by injecting doxorubicin whereas the control group was administered 0.9% saline. The pretreatment of the other three experimental groups was carried out with alpha tocopherol, carvedilol, and metformin for 11 days prior to doxorubicin injection. Blood sampling was taken on the 12th day for biomarkers and slides of heart sections were made for microscopic examination.

Results: Doxorubicin caused marked myocardial damage portrayed by elevation of serum biomarkers levels like cTnI, CK-MB and LDH, and severe necrosis of cardiac cells. Concurrent treatment with α -tocopherol, carvedilol and metformin led to reduced serum levels of these biomarkers with improved histopathological images, more obvious in carvedilol and metformin groups.

Conclusion: The use of carvedilol, metformin, and α -tocopherol can mitigate cardiac adverse effects doxorubicin. The quantitative estimation of serum cTnI may prove cost-effective by identifying extent of cardiac injury at subclinical stage.

Keywords: Doxorubicin, cardiac troponin I, lactate dehydrogenase, LDH, creatine kinase-MB.

INTRODUCTION

Doxorubicin (Dox), one of the most potent FDA approved chemotherapeutic agent is extensively used to treat large number of solid and hematological cancers with significant long-term cancer survival, but related cardiotoxicity limits its use in full therapeutic doses.¹ Doxorubicin kills cancer cells by DNA intercalation and inhibits their replication targeting the required Topoisomerase II enzyme by its unique chemical structure. It creates DNA adducts with subsequent DNA damage leading to apoptosis of cancer cells.²

Dox semiquinone iron containing unstable metabolites generate reactive oxygen species (ROS) and free radicals. The cardiac cells are innately sensitive to these reactive species. The highly reactive oxidized metabolites cause nuclear and mitochondrial DNA lesions in cardiac cells, increasing release of calcium from sarcoplasmic reticulum, thus ruining the myofibril architecture and cellular proteins. The resulting apoptosis or necrosis of cell, release cardiac troponins I (cTnI) and biomarkers into the blood.³ cTnI is myocardial regulatory protein and is present only in myocardium in large amounts compared to specific CK-MB. cTnI, when estimated quantitatively in serum identifies the cardiac damage at initial phases, substantially much before any other diagnostic method can confirm this.^{4,5}

Dox causes acute toxicity in almost 40% of patients while

subacute to chronic toxicity leads to congestive heart failure in about 28-62% of patients. To date, no definite treatment exists for patients diagnosed with dox-induced cardiomyopathy.⁶ Monitoring of cardiac function and follow-up at regular intervals of patients receiving doxorubicin involves high financial costs.⁷

Alpha-Tocopherol, a type of vitamin E, is inexpensive fat-soluble organic compound. It is believed to prevent redox reactions and related damage in cellular membranes. Its ability to inhibit lipid oxidation alleviates oxidative stress and cardiac toxicity produced by various chemotherapeutics like Dox has been reported.⁸ Carvedilol, having multitude of actions blocking (α) alpha and (β) beta adrenergic non-selectively, has antioxidant, antiproliferative and antiapoptotic effects. It possesses vasculo- and cardioprotective effects.⁹ It has more potent antioxidant activity than Vit E.¹⁰

Metformin, a synthetic biguanide, has been in use worldwide since 1958 to treat diabetes mellitus, with multiple off-label uses.¹¹ It has been reported to block the expression of ferritin heavy chain in cardiac cells responsible for oxidative stress and free radical generation -a principal cause of cardiac damage. It decreases lipid peroxidation, increases the levels of glutathione in heart tissue, modulates mitochondrial ion channels and reinstates its bioenergetics.¹² The aim of this study was to evaluate protective effects of alpha

tocopherol, carvedilol, and metformin on early detection of myocardial damage caused by Dox.

METHODOLOGY

This randomized in-vivo study was performed from Oct 2021 to March 2022 at Department of Pharmacology & Therapeutics, Wah Medical College. The study was approved by Center for Research in Experimental and Applied Medicine (CREAM) at Army Medical College, Rawalpindi. Thirty healthy adult male rabbits were obtained from the market, along with several reagents and medications such as doxorubicin HCL, α -tocopherol, metformin, CK-MB and LDH commercial kits from Merck. Carvedilol from Ferozsans and cTnI Beckman Coulter kit was bought from PMA.

Animals were divided randomly into five groups. Control Group (Gp-C: n=6) was administered daily 02 ml of normal saline solution orally by gavage for whole period of study. Experimental Group (Gp-DE: (n=6) was injected Doxorubicin in a dose of 12 mg/kg body weight (BW) intravenously into marginal vein on rabbit's ear on eleventh day of experiment. Other groups designated as Gp-DA: (n=6) received α -tocopherol, Gp-DC (n=6) carvedilol 30 mg/kg BW and Gp-DM (n=6) metformin 250 mg/kg BW orally for continuous 11 days and these animals were injected Dox in a single dose of 12 mg/kg BW on the eleventh day by intravenous route.

The blood samples for estimation of biomarker were drawn from rabbit's ear at the start and on the last day 24 hours post doxorubicin exposure. All rabbits were weighed and slaughtered on the last day and hearts were taken out and slides prepared for histological study.

The human and rabbit CK-MB sequences and cTnI

antibodies are quite similar. cTnI was quantified using chemiluminescence. The kit provider established a cut-off value of 0.50 ng/ml for cTnI to diagnose cardiac injury. Biochemical tests were carried out in Chemical Pathology Department of AMC while histopathological study of heart slides was done in Lab of POFs Hospital Wah Cantt.

Statistical Analysis: Data were analyzed using SPSS version 22. One Way ANOVAs and Chi Square tests were used. A $p < 0.05$ was deemed significant.

RESULTS

The rabbits in control Gp-C gained weight by $11.52 \pm 2.67\%$, however Gp-E animals showed a fall of $24.88 \pm 2.00\%$. The animals in Gp-DA, Gp-DC and Gp-DM (receiving both doxorubicin and alpha-tocopherol, carvedilol and metformin respectively) displayed less fall in weight as compared to Gp-E.

Cardiac troponin I levels increased grossly up to 10.20 ± 0.00 among rabbits of Gp-E while cTnI levels in Gp-DA, Gp-DC and Gp-DM (3.2 ± 1.00 , 2.24 , and 2.35 ± 1.00 ng/l) were much low as compared to Gp-E, although quite raised when matched with levels of group-C with significant value of ($p < 0.00$) (Table 1& Fig. 1). Serum LDH and CK-MB showed notably elevated values in experimental Gp-E in comparison to control Gp-C, Gp-DA, Gp-DC and Gp-DM with value of p less than 0.005 (Table 1).

Fig-2(a) shows hearts from Gp-C with normal morphology (0 grade necrosis). However, in the experimental group, all slides showed signs of immense necrosis displaying disrupted and broken nuclei with vacuolization, massive neutrophil infiltration, and

Table 1: Comparative values of serum parameters in all groups.

Days	0 Day					12 Day				
Parameters	Gp-C	Gp-E	Gp-DA	Gp-DC	Gp-DM	Gp-C	Gp-E	Gp-DA	Gp-DC	Gp-DM
LDH	745	750	643	760	756	720	1027	460	432	434
SEM $\pm$	25	37	28	34	39	36	115	27	23	21
p value	0.01									
CKMB	121	148	120	167	165	130	446	220	150	135
SEM $\pm$	10	15	11	16	15	9	37	6	4	4
P value	0.00									
CTnI	0.03	0.03	0.04	0.04	0.03	0.03	10.5	3.20	2.24	2.35
SEM $\pm$	0	0	0	0	0	0	0	0	0	0
p Value	0.00									

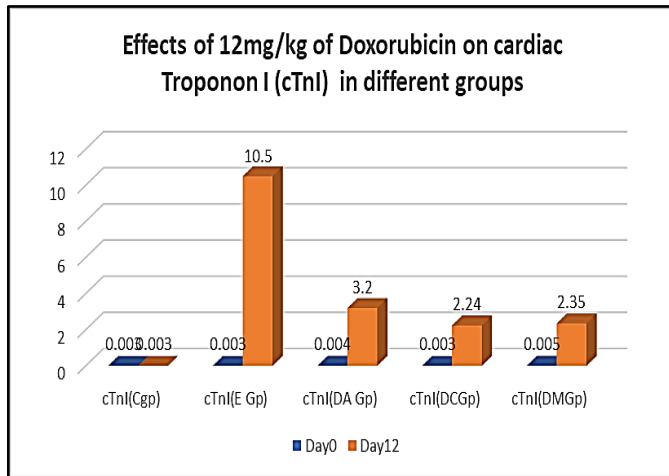


Fig. 1: Levels of cTnI in different groups.

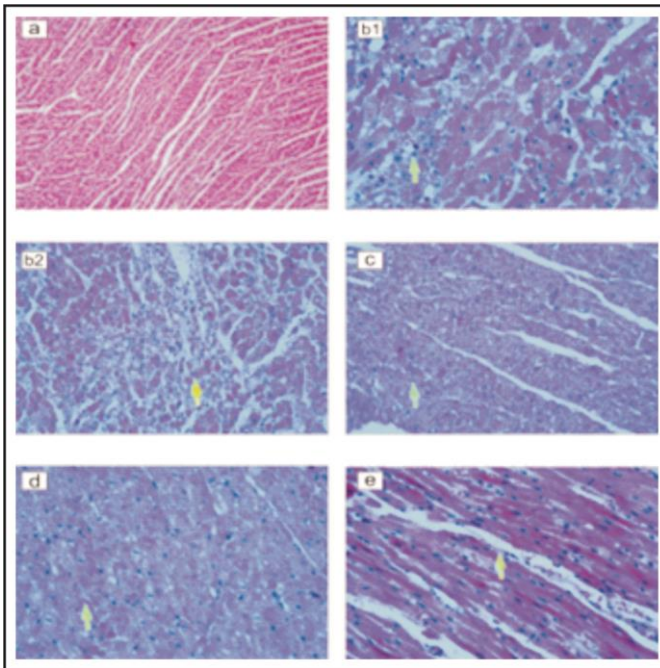


Fig. 2: Histological slices of rabbit cardiomyocytes stained with Hematoxylin and Eosin. From top left clockwise, (a) Gp-C normal, (b1 & b2) Gp-E showing immense necrosis, (c) Gp-DA moderate damage while (d) & (e) Gp-DC and Gp DM show near to normal histology as compared to Gp-E.

myofibril derangement Figure 2 (b1 & b2). Groups DA, DC and DM animals treated with dox plus alpha tocopherol, carvedilol, and metformin respectively showed less myocardial damage depicted by improved histological picture fig 2c, 2d, and 2e. Applying chi square to all the groups revealed statistically significant differences between them ($p=0.009$).

DISCUSSION

Doxorubicin triggered cardiac injury was exhibited by

highly disturbed serum biomarkers and severe Grade 4 necrosis in slides of heart sections in experimental group designated as Gp-E with a significant difference to control Gp-C. These changes were similar to observations in many studies after using Dox in same pattern of doses in rabbits.^{13,14} High levels of these biomarkers and similar histological description were documented by other researches who had reported in both in vivo and in vitro preclinical studies.¹⁵⁻¹⁷

Almost 20% of patients develop severe cardiac adverse effects with Dox.¹⁸ Specific biomarker cTnI senses the occurrence of cardiac insult at initial subclinical stages, substantially before any other diagnostic method reveals the functional defects.

The animals in Gp-DA, Gp-DC and Gp-DM pre-treated with α -tocopherol, carvedilol and metformin for 11 consecutive days prior to administration of doxorubicin on day 12, showed decrease in levels of cTnI, CK-MB and LDH and were ($p<0.000$) significant as compared to Group-E. Histological changes were also comparable with significant difference ($p<0.05$). The morphology grades also changed from necrosis observed towards normality. Our findings are consistent with in vivo research study carried out by Moustafa et al.¹⁹ In rabbits, α -tocopherol presented its effectiveness in alleviating acute and chronic cardiac toxicity and reducing myocardial damage.²⁰

Zhang et al, reported beneficial effects of carvedilol on atrial myocytes in ex-vivo study.²¹ An in vitro study on cultured cardiac muscle cells recognized, decreased cell death when pre-treated with carvedilol.²² The carbazole moiety in its structure provides marked protection in ischemic myocardium and other chronic pathological processes associated with chemotherapeutic insults improving cardiac functions.¹⁰

Metformin has been reported to prevent oxidative stress and increases the levels of glutathione in heart tissue, modulates mitochondrial ion channels and reinstates its bioenergetics.¹¹ It decreases glucose metabolism via aerobic glycolysis beneficial for attenuation of Dox-induced cardiotoxicity. Metformin therapy has been noted for increased survival by cardiac remodeling in post infarction patients.¹² It has been used in radio- and chemotherapy induced cardiac toxicity.²³

CONCLUSION

Pretreatment with α -tocopherol, carvedilol and metformin reduced the doxorubicin induced rendering them more effective. This in vivo study establishes that quantitative estimation of cTnI can help oncologists and cardiologists to plan an appropriate intervention at earlier subclinical stage.

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REFERENCES

- Johnson-Arbor K, Dubey R. Doxorubicin: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023.
- Henriksen PA. Anthracycline cardiotoxicity: An update on mechanisms, monitoring and prevention. *Heart* 2018;104:971–7.
- Ajmal K, Ajmal M, Afzal A, Saima, Naeem U, Sikandar A. Comparison of protective effects of carvedilol and α -tocopherol on doxorubicin-induced cardiotoxicity. *IJBCP* 2019;8:1944–50.
- Anusha V, Sandur VR, Khan S. A review of chemical tools for induction of cardiotoxicity. *Drug Invention Today* 2020;14:370–5.
- Attina G, Triarico S, Romano A, Maurizi P, Mastrangelo S, Ruggiero A. Serum biomarkers for the detection of cardiac dysfunction in childhood cancers receiving anthracycline-based treatment. *BJP* 2022;15:1311–21.
- Cai F, Luis MA, Lin X, Wang M, Cai L, Cen C, et al. Anthracycline-induced cardiotoxicity in the chemotherapy treatment of breast cancer: Preventive strategies and treatment (Review). *Mol Clin Oncol* 2019;11:15–23.
- Proskuriakova E, Jada K, Kakieu Djossi S, Khedr A, Neupane B, et al. Mechanisms and Potential Treatment Options of Heart Failure in Patients with Multiple Myeloma. *Cureus* 2021;13:e15943.
- de Oliveira VA, Monteiro Fernandes AN, dos Santos Leal LM, Ferreira Lima PA, Silva Pereira AR, Pereira IC, et al. α -tocopherol as a selective modulator of toxicogenic damage induced by antineoplastic agents' cyclophosphamide and doxorubicin. *JTEHS* 2023;86:87–102.
- Ahmad R, Hasan IH, Mahmoud AM. Liposomal resveratrol and/or carvedilol attenuate doxorubicin-induced cardiotoxicity by modulating inflammation, oxidative stress and S100A1 in rats. *Antioxidants* 2020;9:159–64.
- Zhan TD, Daniyal MD, Li JD, Mao YD. Preventive use of carvedilol for anthracycline-induced cardiotoxicity: a systematic review and meta-analysis of randomized controlled trials. *Herz* 2020;45:1–4.
- Jung-Min Yu, Mao-Chih Hsieh, Lei Qin, Jiaqiang Zhang, Szu-Yuan Wu. Metformin reduces radiation-induced cardiac toxicity risk in patients having breast cancer. *Am J Cancer Res* 2019;9:1017–26.
- Ajzashokouhi A, Bostan H, Jomezadeh V, Hayes A, Karimi G. A review on the cardioprotective mechanisms of metformin against doxorubicin. *HET* 2020;39:237–48.
- Gava FN, Zacché E, Ortiz EM, Champion T, Bandarra MB, Vasconcelos RO, et al. Doxorubicin induced dilated cardiomyopathy in a rabbit model: An update. *Res Vet Sci* 2013;94:115–21.
- Che FF, Liu Y, Xu CG. Schisandrin B prevents doxorubicin-induced cardiotoxicity in rabbits. *J Sinchuan Univ* 2010;41:24–6.
- Cardinale D, Iacopo F, Cipolla CM. Cardiotoxicity of Anthracyclines. *Front Cardiovasc Med* 2020;7:3–5.
- Sawyer DB, Zuppinger C, Miller TA, Eppenberger HM, Suter TM. Modulation of anthracycline-induced myofibrillar disarray in rat ventricular myocytes by neuregulin-1beta and anti-erbB2: potential mechanism for trastuzumab-induced cardiotoxicity. *Circulation* 2002;105:1551–4.
- Attina G, Triarico S, Romano A, Maurizi P, Mastrangelo S, Ruggiero A. Serum Biomarkers for the Detection of Cardiac Dysfunction in Childhood Cancers Receiving Anthracycline-Based Treatment. *Biomed Pharmacol J* 2022;15. doi.org/10.13005/bpj/2468
- Howlader N, Noone AM, Krapcho M, Miller D, Brest A, Yu M, et al. SEER Cancer Statistics Rev 2019;1975–2016.
- Moustafa I, Saka S, Viljoen M, Oosthuizen F. Vitamin E and levocarnitine as prophylaxis against doxorubicin-induced cardio toxicity in the adult cancer patient: A review. *JOPP* 2022;28:1388–99.
- Milei J, Boveris A, Llesuy S. Amelioration of adriamycin-induced cardiotoxicity in rabbits by prenylamine and vitamins A and E. *Am Heart J* 1986; 111:95–102.
- Zhang QL, Yang JJ, Zhang HS. Carvedilol (CAR) combined with carnosic acid (CAA) attenuates doxorubicin-induced cardiotoxicity by suppressing excessive oxidative stress, inflammation, apoptosis and autophagy. *Biomed Pharmacother* 2019;109:71–83.
- Xuan H. Hu, Li, Di Ren, Yi Tan, Jimei Chen, Lei Yang, et al. The cardioprotective effects of carvedilol on ischemia and reperfusion injury by AMPK signaling pathway. *Biomed Pharmacother* 2019;117:109106.
- Mustafa A, Kazım Ü, Mehmet F.S, Abdullah Ö, DeryaKt, Zeynep, et al Cardioprotective effect of metformin against doxorubicin cardiotoxicity in rats. *Anatol J Cardiol* 2016;16:234–41.

Approaches and interventions for postoperative pain management: A comprehensive review

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Objective: To explore pharmacological and non-pharmacological techniques and interventions for managing postoperative pain.

Methodology: This narrative review synthesizes evidence from a range of studies to provide a comprehensive understanding of current practices and emerging trends in postoperative pain management.

Results: Pharmacological approaches include opioids, nonsteroidal anti-inflammatory drugs, and adjuvant medications. The review examines the role of patient-controlled analgesia and regional anesthesia techniques such as epidural analgesia and peripheral nerve blocks.

Non-pharmacological techniques, including acupuncture, relaxation techniques, and cognitive-behavioral interventions are highlighted for their potential benefits and limitations.

Conclusion: Effective postoperative pain management requires a multimodal approach, combining pharmacological and non-pharmacological interventions to optimize patient outcomes.

Keywords: Postoperative pain, analgesics, patient-controlled analgesia, regional anesthesia, complementary therapies.

INTRODUCTION

Postoperative pain management is a critical aspect of patient care, aiming to alleviate pain and improve overall outcomes following surgical procedures. Pain not only causes distress and discomfort but can also have far-reaching consequences on patient recovery and well-being. Effective postoperative pain management plays a pivotal role in ensuring optimal patient outcomes, including enhanced comfort, early mobilization, reduced complications, and improved overall satisfaction.¹

Postoperative pain is a common occurrence following surgical interventions. It arises from the intricate interplay of peripheral and central mechanisms triggered by tissue trauma, inflammation, and nerve sensitization. The intensity and duration of pain can vary widely, depending on factors such as the type of surgery, individual pain thresholds, and pre-existing comorbidities. Uncontrolled pain can significantly impact the patient's physical and psychological well-being, leading to prolonged hospital stays, delayed functional recovery, impaired quality of life, and increased healthcare costs.²

Uncontrolled pain interferes with crucial aspects of recovery, such as wound healing, respiratory function, and gastrointestinal motility.³ Untreated or undertreated pain can lead to a cascade of physiological and psychological consequences, including increased stress response, impaired immune function, sleep disturbances, and the development of chronic pain syndromes.⁴ Successful pain management can positively impact the

patient's emotional well-being, reduce anxiety, and enhance overall postoperative recovery.⁵ In this comprehensive review, the aim was to explore the various approaches and interventions for managing postoperative pain.

METHODOLOGY

A literature search was performed using electronic databases such as PubMed, Scopus, and the Cochrane Library. Search terms included "postoperative pain," "analgesics," "patient-controlled analgesia," "regional anesthesia," and "complementary therapies." The search was limited to articles published in English within the last ten years to capture recent developments in the field.

Selection of relevant literature: Articles were selected if they provided substantial information on either pharmacological or non-pharmacological interventions for postoperative pain management. Preference was given to studies that discussed the efficacy, side effects, and patient outcomes related to these interventions. Full-text versions of the selected articles were reviewed to ensure they met the inclusion criteria. Articles were included if they addressed postoperative pain management, discussed pharmacological and/or non-pharmacological interventions.

Key information was extracted from the included articles, focusing on the types of interventions used, their reported efficacy, potential side effects, and patient satisfaction. This extraction aimed to capture the breadth of approaches and the nuances of their application in clinical

practice.

Narrative synthesis: This involved summarizing and discussing the various approaches to postoperative pain management, highlighting the main findings, and identifying common themes and emerging trends. The narrative synthesis allowed for a comprehensive overview of the topic, integrating findings from different studies to provide a holistic understanding of current practices and potential future directions.

Quality considerations: While this review is narrative in nature, attention was paid to the methodological quality of the included studies. Articles with clear, well-reported methodologies and robust data were given more emphasis. The goal was to provide a balanced overview of the literature, recognizing both well-supported findings and areas where further research is needed.

RESULTS

Mechanisms of postoperative pain: At the spinal cord level, pain signals undergo modulation and amplification through various mechanisms, including central sensitization. Central sensitization involves an enhanced response of neurons in the spinal cord to nociceptive input, leading to an increased perception of pain. Additionally, surgical trauma can cause nerve injury, resulting in neuropathic pain characterized by abnormal neuronal excitability and altered pain processing. Understanding the intricate mechanisms underlying postoperative pain is crucial for developing targeted interventions and optimizing pain management strategies.⁶

Neurobiology of pain transmission and perception: The transmission and perception of pain involve complex neurobiological processes that span across multiple regions of the central nervous system (CNS). Nociceptive signals from peripheral tissues are transmitted to the CNS through two main pathways: the spinothalamic tract and the trigeminal system. Within these pathways, nociceptive information is relayed from the spinal cord or trigeminal nucleus to higher brain centers, including the thalamus and the somatosensory cortex. In addition to the primary somatosensory pathways, pain signals can also be modulated by descending inhibitory pathways originating from various brain structures, such as the periaqueductal gray and the rostroventromedial medulla. These descending pathways release endogenous opioids and other neurotransmitters that can inhibit or modulate pain transmission.^{7,8}

Tools and scales for assessing pain intensity and characteristics: Various tools and scales have been developed to assess pain intensity and characterize its qualities. One widely used tool is the Numeric Rating Scale (NRS), which asks patients to rate their pain on a

numerical scale from 0 to 10, with 0 representing no pain and 10 representing the worst imaginable pain.⁹ The NRS provides a simple and quantifiable measure of pain intensity. Similarly, the Visual Analog Scale (VAS) involves patients marking their pain level on a 10 cm horizontal line, with one end representing no pain and the other end representing the worst pain imaginable.

Verbal Rating Scales (VRS) use descriptive terms such as “no pain,” “mild pain,” “moderate pain,” and “severe pain” to categorize pain intensity. These scales allow for quick and efficient pain assessment. Additionally, to capture the multidimensional nature of pain, tools such as the McGill Pain Questionnaire and the Brief Pain Inventory assess pain qualities such as sensory, affective, and evaluative components (Fig.). The choice of pain assessment tool depends on factors such as patient age, cognitive abilities, and cultural background, as well as the specific objectives of the assessment.¹⁰

Subjective and objective measures of pain assessment: Pain assessment encompasses both subjective and objective measures to provide a comprehensive understanding of the pain experience. Subjective measures rely on self-report by patients and involve tools such as the scales mentioned earlier. These self-report measures consider the individual's perception and interpretation of pain. However, challenges can arise when assessing pain in certain patient populations, such as pediatric and geriatric patients. In these cases, objective measures can be employed in conjunction with subjective assessments to enhance accuracy.

Objective measures include physiological indicators, such as heart rate, blood pressure, respiratory rate, and facial expressions. Observational tools, like the Behavioral Pain Scale and the FLACC (Face, Legs, Activity, Cry, Consolability) scale, can help assess pain in nonverbal or cognitively impaired patients. These objective measures provide valuable supplementary information to support pain assessment in individuals who may have difficulty expressing their pain experiences verbally. It is important to consider the limitations and strengths of both subjective and objective measures to obtain a comprehensive and accurate assessment of postoperative pain in diverse patient populations.¹¹

Analgesic medications commonly used in postoperative pain: Effective postoperative pain management often involves the use of various analgesic medications to alleviate pain and improve patient comfort. One commonly used class of analgesics is opioids, such as morphine, oxycodone, and hydromorphone. Opioids exert their analgesic effects by binding to opioid receptors in the central nervous system, inhibiting pain transmission and modulating the

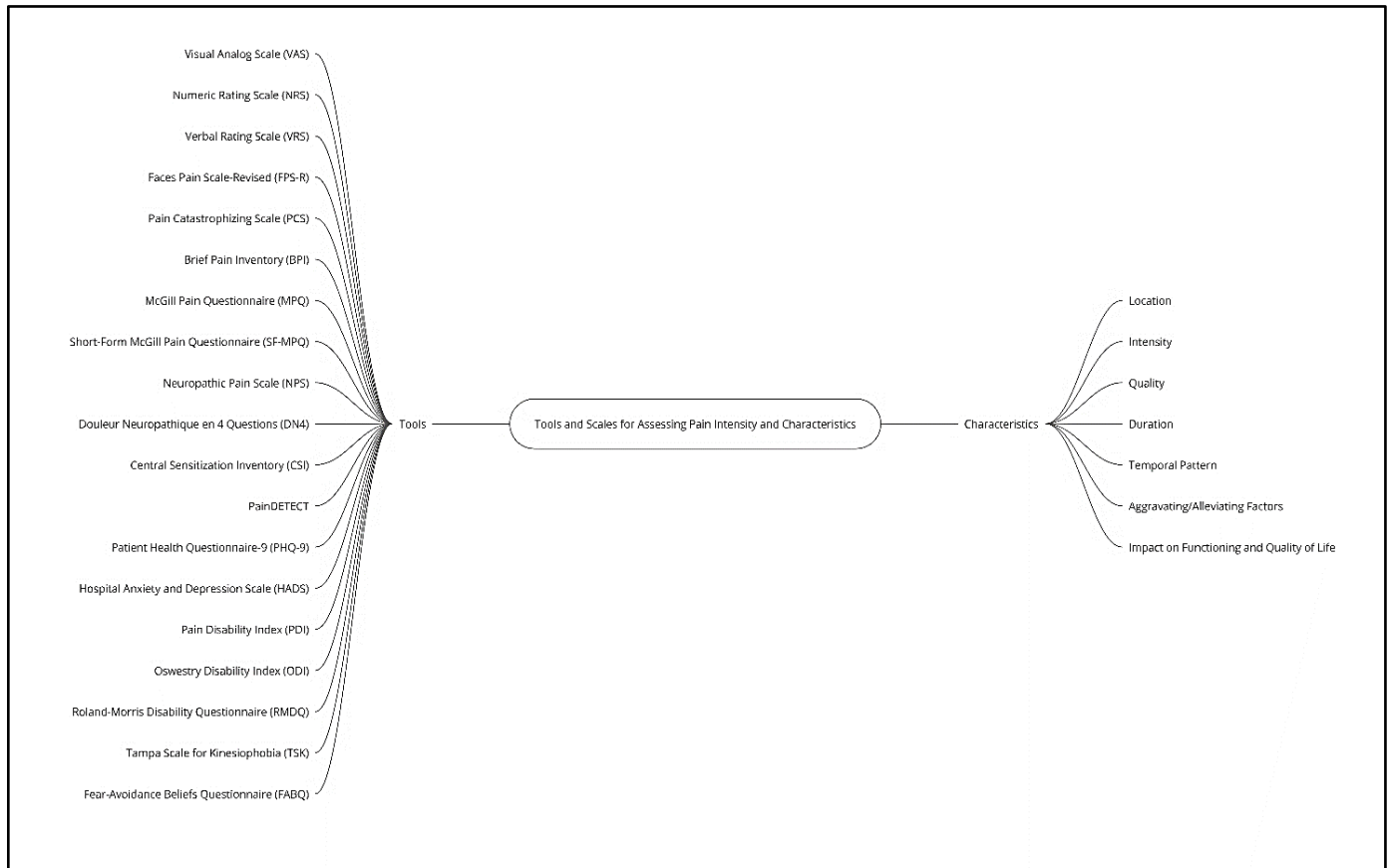


Figure 1: Tools and Scales for assessing pain intensity and characteristics.

perception of pain. While opioids provide potent pain relief, they are associated with potential side effects, including sedation, respiratory depression, nausea, constipation, and the risk of addiction.

Nonsteroidal anti-inflammatory drugs (NSAIDs) including ibuprofen and ketorolac, work by inhibiting prostaglandin synthesis, reducing inflammation, and providing analgesic effects.¹² They are particularly effective for pain resulting from tissue inflammation, such as that observed in surgical sites. Adjuvant medications, such as anticonvulsants (e.g., gabapentin), antidepressants (e.g., amitriptyline), and local anesthetics (e.g., lidocaine), are often used in combination with opioids or NSAIDs to enhance pain control through their unique mechanisms of action or synergistic effects.¹³

Opioid analgesics: Efficacy, safety, and side effects: These medications bind opioid receptors in the central and peripheral nervous systems, effectively reducing pain transmission and perception. Opioids are highly effective in controlling moderate to severe pain, making them a valuable component of multimodal analgesic regimens. However, it is crucial to carefully consider the efficacy, safety, and potential side effects associated with opioid use.¹⁴ The efficacy of opioids varies depending on factors

such as the specific opioid used, the route of administration, and individual patient characteristics. Long-term use of opioids carries the risk of tolerance, physical dependence, and the development of opioid use disorder. Balancing the benefits of opioid analgesia with the risks and potential side effects requires thoughtful prescribing practices and close monitoring.¹⁵

Patient-controlled analgesia (PCA) and its benefits: It is a non-pharmacological approach that allows patients to self-administer pain medication within predetermined limits. With PCA, patients have control over their pain management by initiating analgesic doses when needed. This approach typically involves an electronic device connected to an intravenous line or a subcutaneous catheter. Patients can trigger the administration of a predetermined dose of analgesic medication by pressing a button.

PCA offers several benefits in postoperative pain management. It provides patients with a sense of empowerment and control over their pain, promoting active involvement in their care. By allowing patients to self-administer medication within preset safety parameters, PCA can help optimize pain relief while minimizing the risk of medication overdose.¹⁶ It

promotes individualized pain management, as the analgesic dose can be adjusted based on the patient's unique needs and response.¹⁷

Regional anesthesia techniques: Epidural, peripheral nerve blocks: Regional anesthesia techniques, such as epidural anesthesia and peripheral nerve blocks, have gained prominence in postoperative pain management. Epidural anesthesia involves the administration of local anesthetic medications into the epidural space, providing effective pain relief by blocking nerve transmission. This technique is commonly used in major abdominal and orthopedic surgeries. They can facilitate early mobilization, reduce the risk of postoperative complications, and contribute to shorter hospital stays. However, the use of regional anesthesia techniques requires expertise in administration, monitoring, and management of potential complications. Appropriate patient selection, accurate placement of the blocks, and vigilant monitoring are crucial to ensure optimal outcomes and patient safety.¹⁹

DISCUSSION

Importance of multimodal analgesia in optimizing pain control: Multimodal analgesia is a key approach in postoperative pain management that involves combining multiple modalities to achieve effective pain control while minimizing the use of any single analgesic agent. This approach recognizes that pain has multiple underlying mechanisms and can be best addressed through a combination of therapies that target different pathways. By using a multimodal approach, clinicians can harness the synergistic effects of various analgesics and techniques to provide superior pain relief.²⁰

For example, combining opioids with non-opioid analgesics, such as NSAIDs or acetaminophen, can reduce the dose and associated side effects of opioids while providing additive or even synergistic pain relief. Additionally, incorporating non-pharmacological approaches, such as PCA, regional anesthesia techniques, and complementary therapies, into the analgesic regimen further enhances pain control and patient comfort. Multimodal analgesia not only improves pain management but also contributes to a reduced risk of opioid-related adverse events, faster recovery, and improved patient satisfaction.²¹

Tailoring pain management strategies to individual patient needs: Every patient's pain experience is unique, influenced by factors such as age, comorbidities, medication history, and surgical procedure. Therefore, tailoring pain management strategies to individual patient needs is essential for achieving optimal pain control. This approach involves a comprehensive assessment of the patient's pain characteristics, preferences, and goals. By

considering individual factors, clinicians can select appropriate analgesic medications, routes of administration, and non-pharmacological interventions.²² For instance, elderly patients may have specific concerns related to polypharmacy and potential drug interactions, warranting a careful selection of analgesics, and monitoring for adverse effects. Pediatric patients may require age-appropriate pain assessment tools, dosage adjustments, and child-friendly non-pharmacological interventions. By tailoring pain management strategies to individual patients, healthcare providers can optimize pain relief, minimize adverse effects, and improve patient satisfaction and overall outcomes.²³

Pediatric postoperative pain management considerations: Managing postoperative pain in pediatric patients requires special considerations due to their unique physiological and developmental characteristics. Children may have difficulty communicating their pain experiences, making accurate pain assessment challenging. Therefore, healthcare providers rely on a combination of subjective and objective measures to evaluate pain, including self-report scales, behavioral observation, and physiological indicators.²⁴

Geriatric patients: Challenges and strategies: Pain management in geriatric patients presents unique challenges due to age-related changes in pharmacokinetics, comorbidities, and the increased likelihood of polypharmacy. Geriatric patients may experience altered drug metabolism, decreased renal function, and increased sensitivity to medications.

Strategies for preventing and managing Opioid-related adverse events: Given the potential for opioid-related adverse events, it is crucial to implement strategies to prevent and manage these complications. Risk assessment tools, such as the Opioid Risk Tool (ORT) or the Screener and Opioid Assessment for Patients with Pain (SOAPP), can help identify patients at higher risk for opioid-related adverse events, such as addiction or misuse.

Role of pain management in ERAS protocols: Enhanced Recovery after Surgery (ERAS) protocols are comprehensive, evidence-based perioperative care pathways designed to optimize patient outcomes, speed up recovery, and minimize complications.

Multimodal analgesic strategies to facilitate early recovery and reduce complications: Multimodal analgesic strategies are a cornerstone of pain management in ERAS protocols. The goal is to utilize a combination of analgesic medications and techniques to provide effective pain relief while minimizing adverse effects.

CONCLUSION

This comprehensive review has highlighted various aspects of pain management, including the physiology of pain, assessment techniques, pharmacological and non-pharmacological approaches, tailored strategies for special populations, risk mitigation, and emerging trends. By implementing multimodal approaches, engaging patients in shared decision making, and staying abreast of advancements in technology and precision medicine, healthcare providers can enhance pain control, minimize complications, and enhance the overall patient experience. Continued research and collaboration are crucial for further advancements in this critical area of medical surgical nursing.

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REFERENCES

- Parthipan A, Banerjee I, Humphreys K, Asch SM, Curtin C, Carroll I, et al. Predicting inadequate postoperative pain management in depressed patients: a machine learning approach. *PLoS One* 2019;14:e0210575.
- Moussa N, Ogle OE. Acute pain management. *Oral Maxill Surg Clin* 2022;34:35-47.
- Brenner D, Shorten GD, O'Mahony SM. Postoperative pain and the gut microbiome. *Neurobiol Pain* 2021;10:100070.
- Taylor S-S, Noor N, Urits I, Paladini A, Sadhu MS, Gibb C, et al. Complex regional pain syndrome: a comprehensive review. *Pain Ther* 2021;10:875-92.
- Ireland KC, Lalkhen AG. Postoperative analgesia. *Anaesthesia Intensive Care Med* 2019;20:98-104.
- Gulur P, Nelli A. Persistent postoperative pain: mechanisms and modulators. *Curr Opin Anesthesiol* 2019;32:668-73.
- Mota-Rojas D, Napolitano F, Strappini A, Orihuela A, Ghezzi MD, Hernández-Ávalos I, et al. Pain at the slaughterhouse in ruminants with a focus on the neurobiology of sensitisation. *Animals* 2021;11:1085-9.
- Mostofi A, Morgante F, Edwards MJ, Brown P, Pereira EA. Pain in Parkinson's disease and the role of the subthalamic nucleus. *Brain* 2021;144:1342-50.
- Bielewicz J, Daniluk B, Kamieniak P. VAS and NRS, same or different? Are visual analog scale values and numerical rating scale equally viable tools for assessing patients after microdiscectomy? *Pain Res Manag* 2022;2022.
- Shafshak TS, Elnemr R. The visual analogue scale versus numerical rating scale in measuring pain severity and predicting disability in low back pain. *J Clin Rheumatol* 2021;27:282-5.
- Peng T, Qu S, Du Z, Chen Z, Xiao T, Chen R. A systematic review of the measurement properties of face, Legs, activity, Cry and consolability scale for pediatric pain assessment. *J Pain Res* 2023;1185-96.
- Li Jw, Ma Ys, Xiao Lk. Postoperative pain management in total knee arthroplasty. *Orthop Surg* 2019;11:755-61.
- Anger M, Valovska T, Beloeil H, Lirk P, Joshi GP, Van de Velde M, et al. PROSPECT guideline for total hip arthroplasty: a systematic review and procedure-specific postoperative pain management recommendations. *Anaesthesia* 2021;76:1082-97.
- Abdel Shaheed C, Awal W, Zhang G, Gilbert SE, Gallacher D, McLachlan A, et al. Efficacy, safety, and dose-dependence of the analgesic effects of opioid therapy for people with osteoarthritis: systematic review and meta-analysis. *Med J Aust* 2022;216:305-11.
- Franco-de La Torre L, Figueroa-Fernández NP, Franco-González DL, Alonso-Castro AJ, Rivera-Luna F, Isiordia-Espinoza MA. A Meta-analysis of the analgesic efficacy of single-doses of ibuprofen compared to traditional non-opioid analgesics following third molar surgery. *Pharmaceuticals* 2021;14:360-5.
- Motamed C. Clinical update on patient-controlled analgesia for acute postoperative pain. *Pharmacy* 2022;10:22-6.
- Nardi-Hiebl S, Eberhart L, Gehling M, Koch T, Schlesinger T, Kranke P. Quo Vadis PCA? A review on current concepts, economic considerations, patient-related aspects, and future development with respect to patient-controlled analgesia. *Anesthesiology Res Pract* 2020;2020.
- Giaccari LG, Aurilio C, Coppolino F, Pace MC, Passavanti MB, Pota V, et al. Peripheral nerve blocks for postdural puncture headache: a new solution for an old problem? *In Vivo*. 2021;35:3019-29.
- Kamel I, Ahmed MF, Sethi A. Regional anesthesia for orthopedic procedures: What orthopedic surgeons need to know. *World J Orthop* 2022;13:11-5.
- Tong K, Nolan W, O'Sullivan DM, Sheiner P, Kutzler HL. Implementation of a multimodal pain management order set reduces perioperative opioid use after liver transplantation. *Pharmacotherapy: J Human Pharm Drug Ther* 2019;39:975-82.
- Ntalouka MP, Brotis AG, Bareka MV, Stertsou ES, Fountas KN, Arnaoutoglou EM. Multimodal analgesia in spine surgery: an umbrella review. *World Neurosurg* 2021;149:129-39.
- Hodges PW. Hybrid approach to treatment tailoring for low back pain: a proposed model of care. *J Orthop Sport Phys Ther* 2019;49:453-63.
- Cuomo A, Bimonte S, Forte CA, Botti G, Cascella M. Multimodal approaches and tailored therapies for pain management: the trolley analgesic model. *Taylor & Francis*; 2019. p. 711-4.
- Shah P, Siu A. Considerations for neonatal and pediatric pain management. *Am J Health-System Pharm* 2019;76:1511-20.

Role of baricitinib and sotrovimab in the management of COVID-19

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Objective: To review the role of baricitinib and sotrovimab in managing COVID-19, amidst evolving treatment guidelines and varying efficacy against different virus variants.

Methodology: This review utilized online database using specific keywords related to the subject independently performed with manual checks of reference lists for completeness.

Results: Baricitinib, authorized with remdesivir for severe COVID-19, reduces mechanical ventilation and ICU admissions without increasing hospital stays, and shows improved mortality and recovery rates, especially when combined with corticosteroids.

Sotrovimab, effective in early clinical trials at reducing hospitalizations and adverse events, has shown comparable or superior efficacy to other antivirals but lost authorization for variants like Omicron BA.2.

Conclusion: Baricitinib works as a JAK inhibitor with a 2 mg dose recommended for COVID-19, while sotrovimab, a monoclonal antibody, neutralizes SARS-CoV-2 but has limitations against certain variants. Both drugs offer significant benefits in treating severe COVID-19.

Keywords: Baricitinib, COVID-19, guideline, management, sotrovimab.

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a worldwide pandemic caused by the infectious spread of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which has affected the global population.¹⁻³ It had a case-fatality rate of 1-10% among different age groups in different parts of the world, with clinical manifestations of fever, dry cough, anosmia, myalgia, and many more. The varying clinical course of the disease became a major area in research as there were risks of COVID-19 progressing into acute respiratory distress syndrome (ARDS) and death.

When it was announced officially that the method of transmission was through respiratory droplets, preventive measures such as social distancing, quarantine, and mask-wearing are quickly enacted to limit virus spread.¹ The total confirmed cases for Indonesia lie at 6.7 million people, while death reached a rate of 162 per 1000 and there is big change in incidence.⁴⁻⁷

Over the course of the pandemic, many quick authorizations of novel drugs and new approvals of pre-existing antiviral drugs has been enacted due to the state of emergency imposed by COVID-19. The guidelines for treatment keep changing along with recent developments, especially since many variants and sub-variants of COVID-19 is shown to have different susceptibility when treated with the same drug. In the 2023 published COVID-19 rapid guideline by the National Institute for

Health and care excellence (NICE), approved drugs for therapeutic use in COVID-19 include antivirals nirmatrelvir combined with ritonavir (marketed as Paxlovid), remdesivir, and molnupiravir in cases of high-risk of progression towards severe COVID-19.

Corticosteroids, primarily dexamethasone or hydrocortisone/prednisolone when the former is unavailable, is also recommended in the treatment of COVID-19 especially in patient in need of supplemental oxygen or is in hypoxia but not tolerant to supplemental oxygen during the course of their disease to support increase of saturation levels.⁸

A variety of monoclonal antibodies such as sotrovimab and combined casirivimab-imdevimab are also potential therapeutic option. Sotrovimab, currently marketed as Xevudy, is approved for use in patients with an increased risk of severe COVID-19, while avoiding adjuvant combined ritonavir-nirmatrelvir. As for combined casirivimab-imdevimab, although studies show its benefit, it has not been proven effective against the Omicron variants. Due to the low cost-effectivity and unreliable efficacy, the combined agent is no longer recommended.⁸

Another therapeutic option established for COVID-19 include tocilizumab (marketed as RoActemra) and baricitinib (with conditional recommendation), which are drugs used in treating rheumatoid arthritis. Their usage is recommended in patients requiring supplemental oxygen

or those who have been administered corticosteroid. The official guideline from NICE also elaborated on agents that were thought to have some benefits for treating COVID-19 in the community without any prior scientific evidence, including limiting the use of low molecular weight heparins for venous thromboembolism prophylaxis, antibiotics for suspicion of bacterial infections, and disapproving the use of azithromycin, colchicine, and doxycycline, and allowing the use of budesonide, ivermectin, and vitamin D only for research.⁸

METHODOLOGY

This literature review utilized online database through Google from April 19, 2023, to May 4, 2023. Keywords were chosen using terms such as “baricitinib,” “COVID-19,” “2019-nCoV disease,” “2019 novel coronavirus infection,” “guideline,” “management,” “sotrovimab,” and other synonyms. The inclusion criteria for the articles included an article (preferably clinical trial, randomized controlled trial, or systematic review), articles published in English, and articles that were novel (published in the past 5 years) except for which there is no novel articles regarding the topic. The exclusion criteria included articles not available by full-text and articles that showed no relevance to the study. The search was independently conducted by two authors. Reference lists of eligible studies were manually checked to ensure thoroughness.

BARICITINIB

Baricitinib, a Janus kinase (JAK) 1/2 inhibitor approved for rheumatoid arthritis, shows promise for COVID-19 treatment due to its dual effects of reducing cytokine release and potentially inhibiting viral entry. It blocks JAK1/2 signaling and inhibits ACE-mediated endocytosis of SARS-CoV-2, with antiviral effects demonstrated in primary human liver spheroids.^{9,10} A study by Sims et al, revealed its pleiotropic effects, notably decreasing IL-6, MCP-3, IL-10, CXCL10, IFN- γ , PTX3, IL-1RA, MCP-2, CCL19, and IL-18R1.¹¹ These reductions, along with a decrease in neutrophil and plasmacytoid dendritic cell-mediated immune surveillance, suggest that baricitinib may mitigate the cytokine storm and improve clinical outcomes in COVID-19 patients.¹¹

Another study by Bronte et al, also found the reductions of IL-6, MCP-3, IL-10, CXCL10, and IFN- γ levels longitudinally among baricitinib-treated patients with COVID-19, indicating modulation of cytokine storm dynamics. Additionally, changes in PTX3, IL-1RA, MCP-2, CCL19, IL-18R1, sPDL1, and CCL23 were observed, suggesting broader immunomodulatory effects potentially contributing to therapeutic efficacy.⁹ Most

recently, a 2020 clinical trial has elucidated results that authorizes use of baricitinib in synergy with remdesivir to treat emergency hospitalized COVID-19 patients who use invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO). However, its use as a single-agent has not been clinically approved for the management of COVID-19.¹²

A meta-analysis by Chen et al, evaluating 6 cohorts and 5 clinical trials on the administration of JAK inhibitors in COVID-19, one of them being baricitinib, results showed that these inhibitors are able to decrease invasive mechanical ventilation use (RR: 0.63, $p=0.002$), and lower rates of admission into intensive care units (RR: 0.24, $p=0.05$). Baricitinib also does not increase length of hospitalization compared to standard care and it shows a decreased risk of acquiring acute respiratory distress syndrome (RR: 0.5, $p=0.16$).¹³ Results from other meta-analyses showed reduction in patients needing mechanical ventilation (OR: 0.76, $p=0.06$)¹⁴ and improvement in ICU admission (RR: 0.12, $p<0.001$) and oxygenation index outcomes (MD: 104.88, $p<0.001$).¹⁵⁻¹⁷ Breaking it down further, a controlled-trial on baricitinib in COVID-19 by Ely et al, showed that it reduced all-cause mortality in COVID-19 patients compared to placebo in day 28 (hazard ratio/HR: 0.54, $p=0.03$) and day 60 (HR: 0.56, $p=0.027$). A 19% and 17% rate reduction of absolute risk in day 28 and 60, respectively, were also established in the baricitinib group. Recovery observation also showed a higher rate or recovery at day-28 in patients getting baricitinib (37%) compared to placebo (26%).¹⁸

Other than baricitinib's benefit as a single agent in treating COVID-19, four clinical trials had elucidated the benefit of administering baricitinib as an adjuvant to corticosteroids. Study by Wong et al, found that initiating baricitinib in moderate-to-severe patients on dexamethasone had comparable benefits in clinical improvement time, recovery and discharge rate, mortality rate, serious adverse effects, and viral load reduction.¹⁹ Similar results were reported by Roddy et al.²⁰ A comparative study by Rodriguez et al, also found that patients with combined baricitinib and corticosteroids had greater improvement in lung function compared to single corticosteroid treatment,²¹ while So et al, found the administration of baricitinib, dexamethasone, and remdesivir together reduced mortality of COVID-19 patients.²²

SOTROVIMAB

Sotrovimab, a recombinant human monoclonal antibody, targets a conserved SARS-CoV-2 spike protein RBD epitope outside the receptor binding motif, effectively

neutralizing the virus in vitro and reducing disease severity in a hamster model. It's mechanism of action involves binding with high affinity to a specific epitope on the SARS-CoV-2 spike protein receptor-binding domain (RBD), which is crucial for the virus to enter host cells.

By targeting this epitope, sotrovimab blocks viral attachment and entry into cells, thereby neutralizing the virus and potentially reducing viral load and disease severity in infected individuals. This mechanism prevents the virus from replicating and spreading further within the body, aiding in the clearance of infected cells and potentially mitigating the progression of COVID-19.²³

A study by Maher et al, identified biomarkers such as baseline NLR and a 10-gene transcriptomic signature that correlate with increased risk of severe COVID-19 outcomes, with respective sensitivities of 36% and 75% and specificities of 95% and 76%. These biomarkers, including serostatus and viral RNA levels, offer insights into disease severity and response to treatments like sotrovimab, which demonstrated significant normalization effects on these markers in clinical settings.²⁴

Sotrovimab is a novel drug developed during the COVID-19 pandemic, which received its first authorization for emergency use in COVID-19 treatment in May 2021. It is currently classified as a monoclonal antibody, specifically developed to neutralize SARS-CoV-2 virus. Early clinical trials on the drug had shown promising results in reducing death and long hospitalizations in COVID-19 patients, becoming an authorized emergency use drug for treating mild to moderate cases of the respiratory infections.

However, its limitation in treating sub variants of COVID-19, one of them being the omicron BA.2 variant, had ceased its authorization for use in COVID-19. Sotrovimab is injected intravenously or intramuscularly, performing its benefits through a mechanism of inhibiting the internalization of the virus.

CONCLUSION

As established in the COVID-19 rapid guideline (NICE) in 2023, both sotrovimab and baricitinib are approved therapeutic options in the management of COVID-19. Scientific evidence from multiple trials, observation studies, and meta-analyses have shown significant benefits of administering these drugs in improving clinical outcomes of COVID-19 along with quality-of-life for patients. Sotrovimab is proven to be efficacious as a single agent in patients with high-risk of progression towards severe COVID-19, reducing mortality rate, mechanical ventilation use, and overall clinical outcomes. On the other hand, baricitinib is proven to be

effective as a single agent, along as a combined agent with corticosteroids in patients already requiring ventilation. Both drugs perform significant benefits in severe cases, making them important first choice of therapy for COVID-19.

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REFERENCES

1. Chowdhury SD, Oommen AM. Epidemiology of COVID-19. *J Dig Endosc* 2020;11:3–7.
2. Ruslie RH, Darmadi D. Coronavirus disease-19 and mental health. *Open Access Maced J Med Sci* 2020;8:268–71.
3. Siregar GA, Siregar GP, Darmadi D, Ruslie RH. Coronavirus Disease-19 and Liver Injury. *Open Access Maced J Med Sci* 2020;8:154–7.
4. Siregar GA, Siregar GP, Darmadi D. Gastrointestinal Aspects of COVID-19: A Review. *Open Access Maced J Med Sci* 2020;8:52–4.
5. Ruslie RH, Darmadi D, Siregar GA. Paediatric immunization practice during coronavirus disease-2019 pandemic. *Open Access Maced J Med Sci* 2020;8:258–60.
6. Ruslie RH, Darmadi D, Siregar GA. Susceptibility of coronavirus disease-19 in pediatric population. *Open Access Maced J Med Sci* 2020;8:363–5.
7. WHO. WHO Coronavirus (COVID-19) Dashboard. WHO; 2023. Available from: <https://covid19.who.int>
8. The National Institute for Health and Care Excellence (NICE). COVID-19 Rapid Guideline: Managing COVID-19. The National Institute for Health and Care Excellence (NICE); 2023. Available from: <https://www.nice.org.uk/guidance/ng191/resources/covid19-rapid-guideline-managing-covid19-pdf-51035553326>
9. Bronte V, Ugel S, Tinazzi E, Vella A, De Sanctis F, Canè S, et al. Baricitinib restrains the immune dysregulation in patients with severe COVID-19. *J Clin Invest* 2020;130:6409–16.
10. Petrone L, Petruccioli E, Alonzi T, Vanini V, Cuzzi G, Fard SN, et al. In-vitro evaluation of the immunomodulatory effects of Baricitinib: Implication for COVID-19 therapy. *J Infect* 2021;82:58–66.
11. Sims JT, Krishnan V, Chang CY, Engle SM, Casalini G, Rodgers GH, et al. Characterization of the cytokine storm reflects hyperinflammatory endothelial dysfunction in

- COVID-19. *J Allerg Clin Immunol* 2021;147:107-11.
12. Kalil AC, Patterson TF, Mehta AK, Tomashek KM, Wolfe CR, Ghazaryan V, et al. Baricitinib plus Remdesivir for Hospitalized Adults with Covid-19. *N Engl J Med* 2021;384:795-807.
13. Chen C-X, Wang J-J, Li H, Yuan L-T, Gale RP, Liang Y. JAK-Inhibitors for Coronavirus Disease-2019 (COVID-19): A Meta-analysis. *Leukemia* 2021;35:2616-20.
14. Selvaraj V, Finn A, Lal A, Khan MS, Dapaah-Afriyie K, Carino GP. Baricitinib in Hospitalised Patients with COVID-19: A Meta-analysis of Randomized Controlled Trials. *Clin Med* 2022;49:101489.
15. Zhang X, Shang L, Fan G, Gu X, Xu J, Wang Y, et al. The Efficacy and Safety of Janus Kinase Inhibitors for Patients With COVID-19: A Living Systematic Review and Meta-Analysis. *Front Med* 2022;8:800492.
16. Limen RY, Sedono R, Sugiarto A, Hariyanto TI. Janus Kinase (JAK)-Inhibitors and Coronavirus Disease 2019 (Covid-19) Outcomes: A Systematic Review and Meta-analysis. *Expert Rev Anti Infect Ther* 2022;1-10.
17. Lin Z, Niu J, Xu Y, Qin L, Ding J, Zhou L. Clinical Efficacy and Adverse Events of Baricitinib Treatment for Coronavirus Disease-2019 (COVID-19): A Systematic Review and Meta-analysis. *J Med Virol* 2022;94:1523-34.
18. Ely EW, Ramanan AV, Kartman CE, de Bono S, Liao R, Piruzeli MLB, et al. Efficacy and Safety of Baricitinib Plus Standard of Care for The Treatment of Critically Ill Hospitalised Adults with COVID-19 on Invasive Mechanical Ventilation or Extracorporeal Membrane Oxygenation: An Exploratory, Randomised, Placebo-controlled Trial. *Lancet Respir Med* 2022;10:327-36.
19. Wong CKH, Lau KTK, Au ICH, Xiong X, Chung MSH, Leung BYC, et al. Initiation of Tocilizumab or Baricitinib Were Associated with Comparable Clinical Outcomes Among Patients Hospitalized with COVID-19 and Treated with Dexamethasone. *Front Pharmacol* 2022;13:866441.
20. Roddy J, Wells D, Schenck K, Santosh S, Santosh S. Tocilizumab Versus Baricitinib in Patients Hospitalized With COVID-19 Pneumonia and Hypoxemia: A Multicenter Retrospective Cohort Study. *Crit Care Explor* 2022;4:e0702.
21. Rodriguez-Garcia JL, Sanchez-Nievas G, Arevalo-Serrano J, Garcia-Gomez C, Jimenez-Vizuet JM, Martinez-Alfaro E. Baricitinib Improves Respiratory Function in Patients Treated with Corticosteroids for SARS-CoV-2 Pneumonia: An Observational Cohort Study. *Rheumatology* 2021;60:399-407.
22. So JM, Umeh C, Noriega S, Stratton E, Aseri M, Gupta RC. Use of Baricitinib in Combination with Remdesivir and Steroid in COVID-19 Treatment: A Multicenter Retrospective Study. *Cureus* 2021;13:e20620.
23. Russo A, Grimaldi P, Pisaturo M, Onorato L, Coppola N. Efficacy of sotrovimab on omicron BA.2, BA.4 and BA.5 subvariants of sars-cov-2 vs. other early therapies: a systematic review and meta-analysis of literature data. *Front Immunol* 2024;15:1295029.
24. Maher MC, Soriaga LB, Gupta A, Chen YP, di Iulio J, Ledoux S, et al. Antibody therapy reverses biological signatures of COVID-19 progression. *Cell Rep Med* 2022;3.

Unraveling the potential of saliva: Exploring biomarker detection in xerostomia diagnosis

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Saliva is a biological fluid produced by three major and numerous minor salivary glands. It performs several important functions such as aiding in digestion, wound healing, speech, and protection of soft tissues and teeth. The feeling of oral dryness, known as xerostomia, is subjective, but it can be measured objectively by salivary flow rate analysis. Prolonged xerostomia may lead to multiple oral problems. There is considerable variation in saliva composition and flow rate at different times of the day within the same person; therefore, adhering to a standardized protocol for all research

participants is crucial. Saliva has the benefits of being rich in proteins and peptides which bottom-up or top-down proteomic techniques can identify. These proteins might be specific to xerostomia and could assist patients and caregivers in effectively monitoring and managing the condition using a kit for at-home point-of-care use, which, in turn, will help in ensuring a better oral health-related quality of life.

Keywords: Biomarker, mouth dryness, proteins, salivary glands, salivary flow rate.

INTRODUCTION

Xerostomia, a multifaceted condition, manifests variably in individuals, sometimes presenting independently of reduced salivary secretions, or conversely, with reduced secretions.¹ Its etiologic encompasses diverse factors such as aging, medication use, medical conditions, psychological states like anxiety and stress, depression, and exposure to radiation in the oro-facial region. Estimates suggest an overall prevalence of xerostomia at 23%, yet considerable heterogeneity exists among study findings.²

Specifically, xerostomia attributed to diminished salivary gland function results in marked oral dryness due to insufficient saliva production. Notably, when xerostomia coexists with clinical indicators of glandular hypofunction, salivary flow rates typically diminish by 40 to 50%.³ Extended xerostomia can precipitate various oral conditions, significantly impacting oral health-related quality of life. Xerostomia stemming from hyposalivation often leads to compromised clearance of oral microbial agents and food remnants, thereby fostering the development of periodontal disease, fungal infections, recurrent ulcers, and dental caries.

Adequate saliva is important for the maintenance of the integrity of oral tissues. There arises an escalating imperative to pinpoint the molecular biomarkers

indicative of xerostomia before it could lead to multiple oral problems. Currently xerostomia is diagnosed based on clinical examination when the patients report to a dentist with periodontal problems, frequent ulcerations, and caries, at that time it is already too late for a preventive measure. This review provides a detailed description of the potential of saliva as a diagnostic tool for identifying protein biomarkers of xerostomia, highlighting the proteins that have been reported in saliva of xerostomia patients suffering from different medical conditions.

Formation of saliva by salivary glands

The oro-facial region houses three primary salivary glands: the parotid, submandibular, and sublingual glands. The parotid gland, the largest among these glands, resides externally adjacent to the ramus of mandible. Submandibular gland comprises of a superficial and a deep lobe and positioned around the posterior margin of the mylohyoid muscle. The sublingual gland, the smallest of the three glands, is situated within the submucosal layer of the floor of mouth. Additionally, minor salivary glands are dispersed throughout the oral cavity in submucosal layer, except within the hard palate and gingiva.

The excretory duct of the parotid gland, known as

Stensen's duct, originates from its anterior section, traverses the masseter muscle, and ultimately opens into the buccal mucosa. Wharton's duct, arising from the submandibular gland's deep lobe, courses beneath the floor of the mouth, culminating in its opening near the lingual frenum. The secretion from the sublingual gland is discharged through a network of short conduits known as the ducts of Rivinus, which directly open into the floor of the mouth or, alternatively, connect with Wharton's duct.⁴

Types of secreted saliva based on composition

Mucous saliva is viscous, thick and lubricant in nature which has abundant mucin proteins. The parotid gland largely secretes serous saliva, while the minor salivary glands primarily form mucous saliva. Conversely, the submandibular and sublingual glands contribute to the production of mixed saliva, combining both serous and mucous components.⁵ The intricate process of saliva formation and secretion is subject to regulation by distinct centers within the brain, the autonomic nervous system, and gastrointestinal hormones, collectively orchestrating the intricate balance of this vital bodily fluid.⁵

Regulation of saliva secretion

The salivary glands receive innervation from both branches of the autonomic nervous system: sympathetic and parasympathetic. However, the parasympathetic division assumes a primary regulatory role in governing salivary secretion. While stimulation from both nerve systems augments saliva production, the resulting quantity, properties, and underlying mechanisms of secretion vary significantly. Sympathetic nerve stimulation specifically activates adrenergic receptors. This activation leads to vasoconstriction and an increased protein content within the secreted saliva. Conversely, parasympathetic stimulation remains pivotal in orchestrating the overall regulation of salivary secretion, exerting a more dominant influence in this physiological process.⁶ Parasympathetic nerve activation prompts vasodilation and a subsequent elevation in blood flow directed towards the salivary glands.

Consequently, this process yields a secretion of watery saliva enriched with ions while exhibiting lower protein content.⁶ Maintaining functional parasympathetic innervation is crucial for supporting the interaction between neurons and epithelial cells, aiding in the repair and regeneration of acinar cells responsible for saliva production in salivary glands. In theory, lesser acini will lead to less saliva production; however, there has not been a notable association between xerostomia, fibrosis,

and atrophy of salivary glands of men in their late fifties. Moreover, xerostomia was negatively correlated with parasympathetic innervation of the connective tissue of these glands, suggesting that reduced parasympathetic innervation impaired the stimuli to salivary acini.⁷

Potential biomarkers in saliva

Whole saliva is a complex oral fluid. The composition of whole saliva is unique, encompassing not only secretions from salivary glands but also constituents like gingival crevicular fluid, epithelial cells, nasal secretions, microorganisms with their byproducts, food residues, blood constituents, and cells involved in inflammation. This fluid comprises roughly 99% water along with a diverse array of electrolytes, proteins, and various small organic compounds such as genetic material, glucose, lipids, and urea. Salivary proteins form a significant part of this complex milieu, encompassing enzymes, immunoglobulins, mucosal glycoproteins, and polypeptides.⁸ Within this intricate matrix, biomarkers—biological molecules measurable and analysable objectively—emerge as crucial indicators of normal biological processes or pathological conditions.

Extensive research has focused on exploring salivary biomarkers as diagnostic and prognostic indicators in many systemic and oral diseases. Their examination in saliva presents a non-invasive and swift diagnostic approach, offering potential importance as crucial diagnostic markers obtainable from patients without invasive procedures. Unstimulated salivary flow rate and flow rate of salivary antimicrobial proteins chromogranin A and lactoferrin are reported to be lower, with higher total protein concentration in elderly patients with subjective xerostomia compared to non-xerostomia controls.⁹

Stress is another important factor to consider in studies about xerostomia. Elevated stress-associated salivary biomarkers such as cortisol and calgranulin A are associated with symptoms of oral dryness and reduced salivary flow.¹⁰ Patients with xerostomia and neuropsychiatric disorders have significantly higher salivary calgranulin A than healthy controls.¹¹ In a pilot study on 29 head and neck cancer patients before and 12 months after radiation therapy, higher levels of lubricating mucin protein 5B (MUC5B) in submandibular saliva had been reported in patients with no or mild xerostomia compared to those with severe xerostomia.¹²

Sjögren's syndrome is an autoimmune disorder associated with lymphocytic infiltration and destruction of salivary and lacrimal glands. In the whole saliva of patients with primary Sjögren's syndrome, certain

secretory proteins are under-expressed such as calgranulin A, carbonic anhydrase VI, cystatins, lysozyme C, polymeric immunoglobulin receptor protein, prolactin-inducible protein, and von Ebner gland protein; or over-expressed such as fructose-bisphosphate aldolase A and α -enolase.¹³ Helper T (Th) 1, 2, and 17 cytokines are significantly higher in the saliva of patients with Sjögren's syndrome compared to healthy controls.¹¹ High salivary B-cell activating factor (BAFF) levels are correlated with increased periodontal pocket depth in patients with complaints of oral dryness with or without primary Sjögren's syndrome and patients with periodontal disease only.¹⁴ Treatment with VIP improved submandibular gland function in Sjögren's syndrome mouse model by downregulating interleukin (IL)-17A expression and enhancing the secretory function of salivary glands by upregulation of aquaporin (AQP)-5.¹⁵ Stress is associated with higher salivary VIP concentration in patients with Sjögren's syndrome and healthy controls in stimulated saliva.¹⁶ The secretion of saliva was increased by upregulation of the expression of AQP-1 in xerostomia patients.¹⁷ Decreased expression of AQP-1 on myoepithelial cells of labial salivary glands in patients with primary Sjögren's syndrome has also been reported.¹⁸ AQP-3 has been proposed to play an important role in saliva secretion and pathogenesis of dry mouth.^{19,20} Moreover, a combination of AQP-3 and AQP-5 expression and intensity of immunoreactivity in labial salivary glands can distinguish between patients with subjective and objective xerostomia, patients with Sjögren's syndrome, and healthy controls.¹⁹ Functionally, it is believed that AQP-5 plays an important role in saliva secretion as it helps in primary saliva production. According to quantitative immunoreactivity, the distinct localization of AQP-5 has been reported in patients with Sjögren's syndrome compared to non-Sjögren's syndrome patients with xerostomia in minor salivary glands analysis.²¹ In a recent study, the expression levels of AQP-4 were proved to be differently expressed; the expression levels of AQP-4 [the ratio of AQP4 to glyceraldehyde 3-phosphate dehydrogenase (GAPDH) RNA] were significantly higher in healthy labial salivary gland samples than in the labial gland samples of patients with primary Sjögren's syndrome.²² The authors reported that the myoepithelial cells in healthy tissues have a strong expression of AQP-4 compared to its expression in the diseased group. It was proposed that the water flow capacity across the myoepithelial cell membrane may be altered in Sjögren's syndrome.²²

Type of saliva samples for biomarker studies

Utilizing oral fluids for detection is particularly advantageous in scenarios requiring extensive screening, bypassing the complexities of blood collection, serum separation, and sample storage, thereby conserving time, effort, and costs. Saliva sampling involves the collection of either stimulated or unstimulated saliva. Stimulated saliva is obtained by introducing a stimulant such as citric acid, malic acid, chewing gum, or paraffin. This type of saliva prominently originates from the parotid gland, followed by other major salivary glands, with minimal input from minor salivary glands.

Conversely, unstimulated saliva, representing the basal flow rate, is collected through methods like drooling, spitting, swabbing, or suction. This saliva continuously safeguards the oral cavity for about 14 hours daily, making it crucial for oral health maintenance. Submandibular and sublingual glands play a substantial role in unstimulated saliva composition, with lesser input from the parotid and minor salivary glands. The secretory contributions from individual glands change post-stimulation; for instance, the parotid gland's serous secretion escalates from 7-8% in unstimulated saliva to more than half in stimulated saliva.²³

Consequently, unstimulated saliva proves more appropriate for biomarker discovery due to its higher protein content, enabling quantitative analysis. In contrast, stimulated saliva is richer in serous secretions. Additionally, research indicates that xerostomia, or dry mouth, exhibits a more pronounced correlation with unstimulated saliva compared to stimulated saliva. Decrease in unstimulated salivary flow rate also corresponded to severe symptoms of dry mouth.²⁴

Salivary flow rate

Individuals with hyposalivation experience reduced oral clearance of sugars and food remnants, thus amplifying their susceptibility to dental caries. This underscores the importance of considering impact of circadian rhythm on salivary flow rates and potentially saliva composition. Therefore, it becomes crucial to uniformly collect saliva samples from all participants at specific times of the day, as this timing could significantly influence the outcomes of studies focused on salivary biomarkers. Consequently, both the quantity and quality of saliva hold equal importance for its surface-related functions, such as lubrication, a pivotal role in which hydration plays a fundamental part.

CONCLUSION

Prolonged xerostomia leads to multiple oral problems including dental caries, periodontal diseases, frequent

fungal infections, recurrent ulcers, burning mouth syndrome, and tongue and lip fissures. These oral problems may be prevented if xerostomia is detected at an early stage for its effective management.

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REFERENCES

- Thomson WM, Ibrahim H, Lyons KM, Foster Page LA, Hanlin SM. Personality, xerostomia and OHRQoL among 35-54-year-olds. *Acta Odontol Scand* 2019;77:114-8.
- Agostini BA, Cericato GO, Silveira ERD. How common is a dry mouth? Systematic review and meta-regression analysis of prevalence estimates. *Braz Dent J* 2018;29:606-18.
- Dawes C. Physiological factors affecting salivary flow rate, oral sugar clearance, and the sensation of dry mouth in man. *J Dent Res* 1987;66:648-53.
- Ellis H. Anatomy of the salivary glands. *Surgery (Oxford)* 2012;30:569-72.
- Pedersen AML, Sorensen CE, Proctor GB, Carpenter GH, Ekstrom J. Salivary secretion in health and disease. *J Oral Rehabil* 2018;45:730-46.
- Holmberg KV, Hoffman MP. Anatomy, biogenesis and regeneration of salivary glands. *Monogr Oral Sci* 2014;24:1-13.
- Sørensen CE, Larsen JO, Reibel J. Associations between xerostomia, histopathological alterations, and autonomic innervation of labial salivary glands in men in late midlife. *Exp Gerontol* 2014;57:211-7.
- de Almeida PDV, Gregio A, Machado M, De Lima A, Azevedo LR. Saliva composition and functions: A comprehensive review. *J Contemp Dent Pract* 2008;9:72-80.
- Mizuhashi F, Koide K, Toya S, Takahashi M, Mizuhashi R, Shimomura H. Levels of the antimicrobial proteins lactoferrin and chromogranin in the saliva of individuals with oral dryness. *J Prosthet Dent* 2015;113:35-8.
- Shigeyama C, Ansai T, Awano S, Soh I, Yoshida A, Hamasaki T, et al. Salivary levels of cortisol and chromogranin A in patients with dry mouth compared with age-matched controls. *Oral Surg Oral Med Oral Path Oral Radiol Endod* 2008;106:833-9.
- Ohshima K, Moriyama M, Hayashida JN, Tanaka A, Maehara T, Ieda S, et al. Saliva as a potential tool for diagnosis of dry mouth including Sjögren's syndrome. *Oral Dis* 2015;21:224-31.
- Dijkema T, Terhaard CH, Roesink JM, Raaijmakers CP, van den Keijbus PA, Brand HS, et al. MUC5B levels in submandibular gland saliva of patients treated with radiotherapy for head-and-neck cancer: a pilot study. *Radiat Oncol* 2012;7:1-4.
- Hu S, Wang J, Meijer J, Jeong S, Xie Y, Yu T, et al. Henry S, Vissink A, Pijpe J, Kallenberg C. Salivary proteomic and genomic biomarkers for primary Sjögren's syndrome. *Arthritis Rheum* 2007;56:3588-600.
- Pers J-O, d'Arbonneau F, Devauchelle-Pensec V, Saraux A, Pennec Y-L, Youinou P. Is periodontal disease mediated by salivary BAFF in Sjögren's Syndrome? *Arthritis Rheum* 2005;52:2411-4.
- Li C, Zhu F, Wu B, Wang Y. Vasoactive intestinal peptide protects salivary glands against structural injury and secretory dysfunction via IL-17A and AQP5 regulation in a model of Sjögren syndrome. *Neuro immunomod* 2017;24:300-9.
- Santavirta N, Kontinen YT, Törnwall J, Segerberg M, Santavirta S, Matucci-Cerinic M, et al. Neuropeptides of the autonomic nervous system in Sjögren's syndrome. *Ann Rheum Dis* 1997;56:737-40.
- Wang Z, Pradhan-Bhatt S, Farach-Carson MC, Passineau MJ. Artificial induction of native aquaporin-1 expression in human salivary cells. *J Dent Res* 2017;96:444-9.
- Beroukas D, Hiscock J, Gannon BJ, Jonsson R, Gordon TP, Waterman SA. Selective down-regulation of aquaporin-1 in salivary glands in primary Sjögren's syndrome. *Lab Invest* 2002;82:1547-52.
- Ichiyama T, Nakatani E, Tatsumi K, Hideshima K, Urano T, Nariai Y, et al. Expression of aquaporin 3 and 5 as a potential marker for distinguishing dry mouth from Sjögren's syndrome. *J Oral Sci* 2018;60:212-20.
- Atif S, Abdul Wahab N, Ghafoor S, Azlina A, Tauseef A, Rana S, et al. Salivary aquaporin-3 as a screening biomarker for xerostomia in patients with periodontal disease and the effects of xerostomia on oral health-related quality of life. *Plos one* 2023;18:e0283995.
- Steinfeld S, Cogan E, King LS, Agre P, Kiss R, Delporte C. Abnormal distribution of aquaporin-5 water channel protein in salivary glands from Sjögren's syndrome patients. *Lab Invest* 2001;81:143-8.
- Sisto M, Lorusso L, Ingravalle G, Nico B, Ribatti D, Ruggieri S, et al. Abnormal distribution of AQP4 in minor salivary glands of primary Sjögren's syndrome patients. *Autoimmunity* 2017;50:202-10.
- Edgar WM. Saliva and dental health. Clinical implications of saliva: Report of a consensus meeting. *Br Dent J* 1990;169:96.
- Márton K, Madléná M, Bánóczy J, Varga G, Fejérdy P, Sreebny LM, et al. Unstimulated whole saliva flow rate in relation to sicca symptoms in Hungary. *Oral Dis* 2008;14:472-7.

Morphological appraisal of the vermiform appendix: A systematic review

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Vermiform appendix (VA) is frequently associated with anatomical variations. However, there remains a contradiction in determining the most prevalent positions of VA despite numerous previous studies. This systematic review examined nine postmortem studies that explored anatomical positions of VA. A comprehensive search was conducted in databases including Cochrane Library, Google Scholar, Web of Science Core Collection, PubMed, and Scopus. Only English-language articles published between January 2013 and December 2022 were considered. The process involved study selection, data extraction, and aggregating the findings. The literature identifies eight distinct types of appendicular positions: retrocecal, pelvic, subcecal, preileal, subileal or promontory, subhepatic, and paracecal. Among these types, the most common are the pelvic and retrocecal positions,

accounting for 38.3% and 34.3%, respectively. Subcecal and postileal positions are less prevalent, with rates of 10.4% and 9.5%, respectively. The remaining types, including subileal/promontory, paracecal, preileal, subhepatic, and others, have prevalence rates of 2.9%, 2.1%, 1.4%, and 1.1%, respectively. Overall, males exhibit a higher incidence of these appendicular positions compared to females. Among postmortem studies, the pelvic position is the most common, representing 38.3% of cases. However, there are no clear theories explaining the differences in VA position between sexes. This study aims to discuss previous research findings on VA morphology and establish terminology for describing its common positions in humans.

Keywords: Vermiform appendix, morphological appraisal, cadaveric review.

INTRODUCTION

Anatomical variations are an integral part of anatomical science. In general, they do not interfere with the function of the human body and do not typically manifest as pathological units, however under certain conditions, these variations can worsen existing pathological states.¹ These variations are termed anatomical variations rather than abnormalities.² The variation types and rate considerably differ from one organ to another.³ Some of them do not impact an individual's physiology, which can be termed normal variations, while others can impact organ function, they are defined as anomalies or malformations.⁴ Clinically, the most important variants are those of brain, heart and the vascular system.⁵ An example of an organ mostly characterized by term of anatomical variations is the vermiform appendix (VA). The VA is a tube-like structure, located in the right quadrant of the abdomen, connected with the cecum exactly below to ileocecal junction. It is covered by the visceral peritoneum known as the mesoappendix, through which the appendicular artery passes to supply the organ.⁶ Understanding the anatomical variations is a basic skill not only of anatomists, but also of clinicians, radiologists, and surgeons.⁷ Despite numerous researchers, there is a

contradiction in determining the most common position of VA, whether is it retrocecal or pelvic. Simply there is a need to define the commonest position of the VA, to gain a good knowledge about it. This study aimed to discuss the findings concerning the morphology of the VA in the previous studies, to define basic term that describe its commonest positions in the human.

METHODOLOGY

Search Strategy: The study included a combination of keywords related to VA such as Morphological variations, anatomical variations, and anatomical positions. The search was limited to studies relevant to anatomical cadaveric data only concerning the VA. We think the cadaveric data are suitable for detecting the appendicular positions because the dissection enables the researcher to see the organ clearly and then it can be studied easily and better, than other studies methods.

Sources of the Data: The data were collected using the following electronic databases: Google Scholar, Cochrane Library, Web of Science Core Collection, PubMed, and Scopus, similar to databases used previously.⁸ English Language Articles were selected, from January 2013 to December 2022. After a

comprehensive check, we found a total of 9 articles that were directly relevant to our research question (Fig. 1).

Inclusion Criteria: The study involved the research conducted on morphological variations, anatomical variations, and anatomical positions of the VA, specifically focusing on gender variation. The review incorporated the studies that described the positions of the free end of the VA in relation to the caecum and terminal part of the ileum, as follows (Table 1):

1. Type I, Retrocecal position: if the free end were found situated behind the cecum, in the 11th clockwise direction.
2. Type II, Pelvic position: if the free end were found directed downward, in a 5th clockwise direction.
3. Type III, Preileal position: if the free end were found situated anterior to the terminal end of the ileum, in the 2nd clockwise direction.
4. Type IV, Postileal position: if the free end were found situated posterior to the terminal end of the ileum, in the 2nd clockwise direction.
5. Type VIII, Promontory/Subileal position: if the free end is found directed downward to the left, on the sacral promontory, in the 4th direction.
6. Type VII, Subhepatic position: if the free end is found directed vertically upward towards with long axis of the ascending colon, at the 12th O'clock wise direction.
7. Type V, Subcecal position: if the free end were found situated under the cecum, in the 7th clockwise direction.
8. Type VI, Paracecal position: if the free end were found laterally to the cecum and ascending colon, at 9th clockwise direction.

Exclusion Criteria: The study excludes the reports on the morphometry of VA, case reports, in addition to imaging and intra-operative studies which report variations relevant anatomical data concerning the VA.

Data Extraction: The data were extracted from the

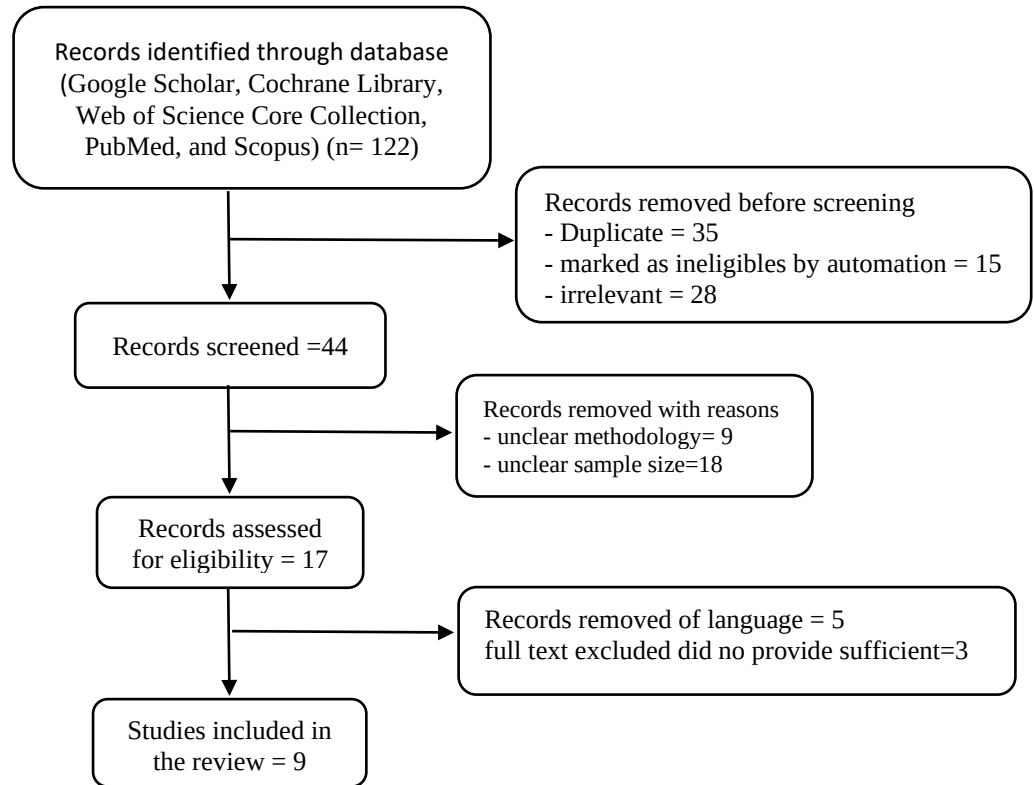


Fig. 1: Diagram outlining the study inclusion process.

selected studies that met the inclusion criteria. The extracted information comprised the following: different types of anatomical positions of the VA, frequencies, and percentages of the positions in male and female cadavers.

Statistical Analysis: The screening of the search results was based on titles, objectives, and study methods, and then the full-text articles that met eligibility criteria were selected. To extract relevant data from the selected studies, we assessed the quality and risk of bias of each included study; then the findings from the selected studies were then aggregated to identify patterns and trends.

RESULTS

Initially, 122 records were identified. After a comprehensive screening of the abstracts, full texts, 113 were removed because of, duplication, irrelevant, full text did not provide sufficient, unclear methodology, sample size, and language. The articles assessed regarding the inclusion criteria were 9 in this review (Fig. 1). A total of 993 dissected cadaver specimens were investigated, 695 were males and 298 were females (Table 2).

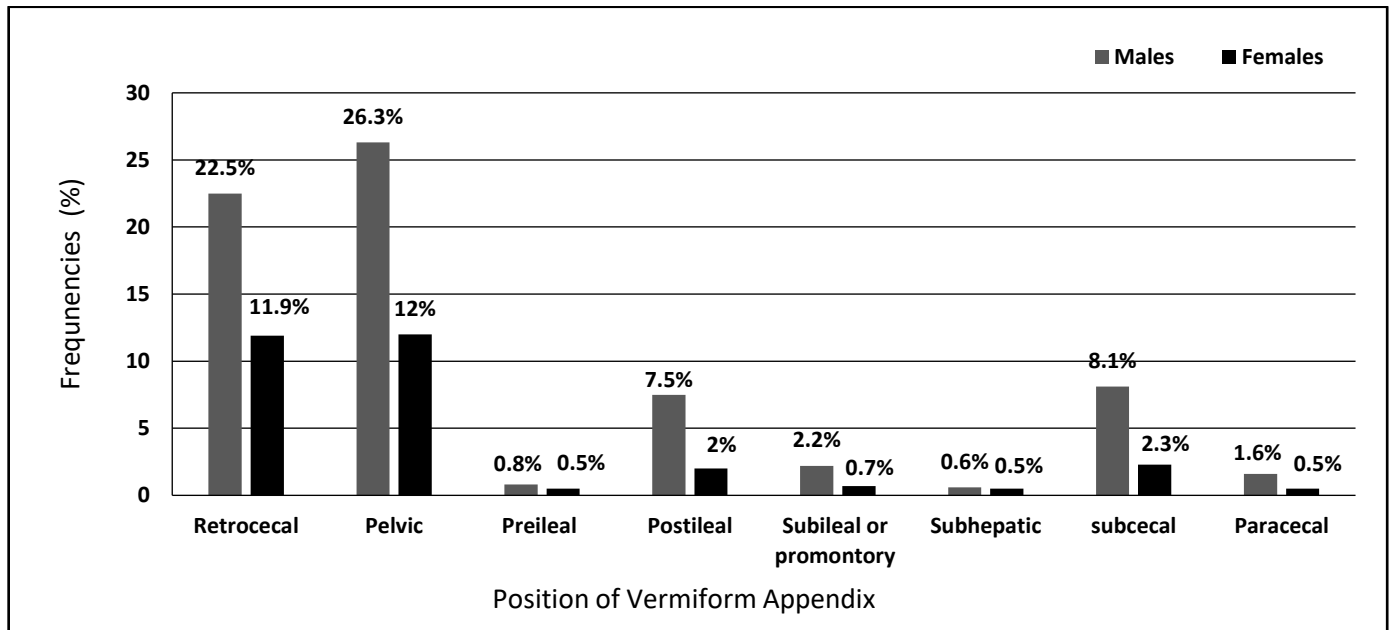
The results of the studies showed that the commonest two types were pelvic and retrocecal followed by subcecal, and postileal (38.3%, 34.3%, 10.4%, 9.5%), respectively, while fewer types were (subileal/promontory, paracecal,

Table 1: Summary of eight types of the vermiform appendix.

Study	Positions of the Vermiform Appendix							
	Retrocecal	Pelvic	Preileal	Postileal	Subileal or Promontory	Subhepatic	subcecal	Paracecal
(Mukul Sarma <i>et al.</i> , 2022) ⁹	66.25%	30%	1.25%	0.0%	0.0%	0.0%	0.0%	2.5%
(Edibamode E. I <i>et al.</i> , 2019) ¹⁰	53.7%	26.8%	2.4%	9.8%	0.0%	0.0%	7.3%	0.0%
(Chaudhari & Kanani 2018) ¹¹	55.5%	23.5%	0.0%	9.0%	0.0%	0.5%	6.5%	5.0%
(Mian Azhar Ahmad <i>et al.</i> , 2017) ¹²	35.95%	41.83%	4.86%	8.87%	0.0%	1.76%	3.89%	2.84%
(Ramanuj Singh1 <i>et al.</i> , 2017) ¹³	61%	21%	8%	2%	0.0%	0.0%	8%	0.0%
(Ehab I. El-Amin <i>et al.</i> , 2015) ¹⁴	60%	35%	1.7%	3.3%	0.0%	0.0%	0.0%	0.0%
(Sanjay Kumar Sinha, Vipin Kumar 2014) ¹⁵	62%	22%	0.0%	0.0%	6%	0.0%	2%	8%
(Philip Mwachaka <i>et al.</i> , 2014) ¹⁶	27%	25%	0.0%	18.8%	18.8%	4.2%	4.2%	2.1%
(Tofighi <i>et al.</i> , 2013) ¹⁷	7%	55.8%	1.5%	12.5%	4.2%	0.0%	19%	0.0%

Table 2: Positions of the vermiform appendix in males and females (n=993).

Gender	No.	Positions of the Vermiform Appendix							
		Retrocecal	Pelvic	Preileal	Postileal	Subileal or Promontory	Subhepatic	Subcecal	Paracecal
Male	695	223(22.5%)	261(26.3%)	8(0.8%)	74(7.5%)	22(2.2%)	6(0.6%)	80(8.1%)	16(1.6%)
Female	298	118 (11.9%)	119(12%)	5(0.5%)	20(2 %)	7(0.7%)	5(0.5%)	23(2.3%)	5(0.5%)
Total	993	341 (34.3%)	380 (38.3%)	14 (1.4%)	94 (9.5%)	29(2.9%)	11(1.1%)	103(10.4%)	21(2.1%)

**Fig. 2: Shows the frequencies & percentage of the positions of the vermiform appendix for males (n=695) and females (n=298) cadavers.**

preileal, and subhepatic) positions, (2.9%, 2.1%, 1.4%, 1.1%), respectively shown in Table 2, Fig. 2.

The pelvic position was the most common variant (26.3% in males and 12% in females), followed retrocecal by (22.5% in males and 11.9% in females), subcecal (8.1% in males and 2.3% in females), and postileal (7.5% in males and 2% in females), subileal or promontory (2.2% in males and 0.7% in females), paracecal (1.6% in males

and 0.5% in females), preileal (0.8% in males and 0.5% in females), and subhepatic (0.6% in males and 0.5% in females). The results showed that, in types of appendicular positions, the males are having a higher incidence than females.

DISCUSSION

The VA is the most common abdominal organ

susceptible to anatomical variations in term of the positions. However, they become clinically and surgically important under certain conditions.¹ Therefore, there are various studies shed light on the VA, most of them focused on the morphological, morphometric, parameters, blood supply, and mesoappendix, using different research methods, such as different imaging types, dissection of the cadavers, and others have studied it intraoperative.^{18,19} This indicates its importance in the medical field because understanding the different positions of the VA is crucial for medical professionals, so, determining the position of the appendix in the postmortem is a reliable way of determining its true location.

Inspite of many previous studies on the position of VA, still there is an incoherence in determining the most common position, whether is it retrocecal or pelvic. The most common two types of VA observed in this study were pelvic and retrocecal, which accounted for almost half of the cases, the pelvic had a higher prevalence than retrocecal. The high prevalence of the pelvic position is similar to previously reported studies,^{20,21} (Fig. 2). Therefore, the findings of the present study are in consonance with that study which stated that the pelvic is more common than the retrocecal, contrary to findings of a previous study,²² which found retrocecal as the most common position in a postmortem. In postmortem studies, the pelvic position appeared to be the commonest, it's suggested that the high frequency of a pelvic VA could be explained on the basis of the embryological development of the caecum and VA, since the VA develops during the descent of the colon, its position can frequently change with the stages of intestinal development.

Moreover, any abnormality of the cecum, such as abnormal rotation or descending of the cecum from the right upper quadrant to the right iliac fossa, and mobile cecum, may play a role in the appendicular locations, and thus fail to take constant position during the development. Therefore, the position of the VA is closely related to the development of the cecum.^{23,24} The displacement of the cecum downward the right iliac fossa, in a similar manner to the VA tends to be deflected downward, toward the pelvic cavity.²⁵

Retrocecal and pelvic positions of the VA may make conditions worse, by providing extra abdominal symptoms, or cause diagnostic confusion. In the pelvic position, the appendix is related to the urinary bladder, the vessels are more likely compressed or kinked in case of an abnormal urinary bladder destination, in the retrocecal position, the appendix is usually hidden by the cecum, the vessels are more likely compressed or kinked by the load of the caecum or the ascending colon. In

addition, if the retrocecal appendix is inflamed, it can cause diffuse peritonitis more than other types, these positions can be regarded as the most susceptible to complication.²⁵

The remaining positions, (subileal or promontory, paracecal, preileal, subhepatic), their occurrence was relatively infrequent in the sample, in the current study, preileal and subhepatic positions are less common, since in none of the reviewed studies such high frequency was found (Table 1). In this series, preileal and subhepatic were the less frequent (1.4%, 1.1%,) however, in most of the reviewed studies (Table 2, Fig. 2), several authors describe this position as less common, especially in non-surgical cases and in older individuals.²⁶

A higher incidence of subhepatic position was observed in the study.²⁷ A high incidence of subhepatic type is rare to occur in the adult and may be found in the fetus in the early stages of development. It indicates the migration of VA from the initial subhepatic or right lumbar region before 30 weeks' gestation to the right iliac fossa after 30 weeks' gestation.

The positions of the free end of the VA reported vary among males and females,²¹ found the pelvic appendix to be the most common in both males and females. A study found pelvic position the most common location of the appendix in both males and females, more frequently seen in females.²⁸

CONCLUSION

This study showed that in postmortem studies pelvic position was the commonest (38.3%). Postmortem studies can provide valuable insights into VA positions more than other study methods. There are no clear theories that explain the differences in the position of the vermiform appendix between the sexes.

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REFERENCES

- David K, Ivan V, Václav B, Vladimír M. Variant Anatomy and Its Terminology. *Medicina* (Kaunas). 2020;56:713-

- 715.
2. Maria Y, Shumaela K, Anum NA, Ayesha A, Nadia A, Ammara G. Variation in Anatomical Position of Vermiform Appendix P J M H S. 2023;17:649-651.
3. Smith HF. Anatomical Variation and Clinical Diagnosis. Diagnostics (Basel). 2021;11:247-52
4. Holmes LB. Current concepts in genetics. Congenital malformations. N Engl J Med. 1976;295(4):204-7.
5. Yammine K. Evidence-based anatomy. Clin Anat. 2014 Sep;27(6):847-852.
6. D'Antoni AV. Clinically Oriented Anatomy, 7th Edition. Keith L. Moore, Arthur F. Dalley, and Anne M. R. Agur (Authors). Baltimore, MD: Lippincott Williams & Wilkins, 2014. Pp. 248-9.
7. Schumpelick V, Dreuw B, Ophoff K, Prescher A. Appendix and cecum. Embryology, anatomy, and surgical applications. Surg Clin North Am. 2000 Feb;80(1):295-318.
8. Jarelnape AA, Ahmed W, Omer S, Fadlala A, Ali Z, Hassan M, et al. Prevalence of smoking cigarettes and beliefs regarding smoking habits among medical students: a cross-sectional study in Sudan. Front Public Health. 2023 Jun 20;11:1193475.
9. Mukul S, Malamoni D, Annie D. Different Positions of Vermiform Appendix in Human Cadavers: A Cross-sectional Study. Int J Anatomy Radiol Surg. 2022;11(3):29-32.
10. Edibamode EI, Adheke MO, Paul JN, Onwuli BC. Morphometric and Morphologic Study of the Vermiform Appendix in Nigerian Cadavers. Saudi J Med Pharm Sci. 2019;5(3):178-181.
11. Chaudhari ML, Kanani S. Anatomical variations of vermiform appendix in Gujarat. Int J Anat Res. 2018;6:4815-4818.
12. Mian AA, Muhammad TA, Nasibullah Z. Variations in the Position and Length of the Vermiform Appendix in Pakistani Population. P J M H S. 2017;11(1):356-361.
13. Ramanuj S, Mousum M, Niraj K, Anjan S. Study on morphological variations of cadaveric vermiform appendix and caecum in Narayan Medical College and Hospital. IAIM. 2017; 4(10):128-132.
14. Ehab E, Gamal YA, Waled AM, Khalid EK, Ashraf ME. Lengths and Positions of the Vermiform Appendix among Sudanese Cadavers. Med Sci. 2015;2(3):222-227.
15. Sanjay KS, Vipin K. Observation on Anatomical Variations of Vermiform Appendix in Kosi Region of Bihar – A Cadaveric Study. J Evidence Based Med Healthcare. 2014;1(8):564-568.
16. Philip M, Hemed E, Simeon S, Julius O. Variations in the Position and Length of the Vermiform Appendix in a Black Kenyan Population. ISRN Anatomy. 2014:1-6. ID 871048.
17. Tofighi H, Taghadosi-Nejad F, Abbaspour A, Behnoush B, Salimi A, Prevalence of Retrocaecal Appendix among Patients with Appendicitis in a Tertiary Care Hospital of Nepal. J Nepal Med Assoc. 2019;57(217):150-153.
18. Singh R, Mahanti M, Kumar N, Sen A. Study on morphological variations of cadaveric vermiform appendix and caecum in Narayan Medical College and Hospital. IAIM. 2017; 4(10):128-132.
19. Sudha KS, Muniappan V. A cadaveric study of anatomical variations in the arterial supply of vermiform appendix. Int J Anat Res. 2017;5(2.1):3777-79.
20. Aragao JA, Aragao LCSA, Aragao FMSA, Lourenco BC, Kuhn CS, Munaretto GF, et al. The anatomical position of the vermiform appendix and its morphometry in relation to the extension of the mesoappendix: a study on fresh cadavers. Revista Científica Multidisciplinar Núcleo do Conhecimento. 2023;8(6):133-144.
21. Mehdi F, Abdolrazagh B, Masoud G, Samira V. Position and Length of the Vermiform Appendix: A Study of 400 Cases in Iranian Population. Govareh. 2022;l 27(3):113-117.
22. Apurba P, Harsimarjit K, Usha C, Adil S, Krzysz B, Artur P, et al. Reappraisal of the variational anatomy of the vermiform appendix and their possible clinical applicability: a cadaveric analysis. Folia Morphologica. 2023. DOI: 10.5603/fm.96443
23. Sadler TW. Longman's Medical Embryology. Capture 14 th, Digestive system. Lippincott Williams and Wilkins, Wolters Kluwer Business, Philadelphia. 2018. Pp 223-230.
24. Keith L, Moore TVN, Persaud MG, Torchia AM. The Developing Human, clinically oriented Embryology. In: Crystal T, editor. The Abdomen, Appendix. 8th Ed. Lippincott Williams and Wilkins, Wolters Kluwer Business, Philadelphia, 2018. Pp. 226-235.
25. Souza SC, Costa SM, Souza ID. Vermiform appendix: positions and length - a study of 377 cases and literature review. J Coloproctol 2015;35,212-216.
26. Tahir I, Amir A, Rab N. Pattern and Positions of Vermiform Appendix in People of Bannu District. Gomal J Med Sci 2012;10(1):100-103.
27. Reshma M, Subhadra DV, Thyagaraju MD, Azharuddin K, Jyothirmayi M. Features and Morphometric Parameters of Human Fetal Vermiform Appendix at Different Gestational Ages. Int J Anat Res. 2013;1(2):18-25.
28. Ghorbani A, Forouzesh M, Kazemifar AM. Variation in Anatomical Position of Vermiform Appendix among Iranian Population: An Old Issue Which Has Not Lost Its Importance. Anat Res Int. 2014;1-4, ID 313575.

Analysis of Curcumin on proliferation, apoptosis and differentiation of hepatocyte mice balb/C exposure to benzapyrene: A Systematic Review

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Objective: To analyse Curcumin effect on proliferation, apoptosis, and hepatocyte differentiation of Balb/C Mice exposed to benzapyrene.

Methodology: A literature search was carried out systematically through the PubMed, NCBI, and Google Scholar databases using keywords, “Curcumin, Proliferation, Apoptosis and Hepatocyte Differentiation of Mice Balb/C, Benzapyrene”. Based on these keywords, the articles obtained were first selected by setting several inclusion criteria.

Results: A total of 550 articles were obtained for the keywords “Curcumin, Proliferation, Apoptosis and Hepatocyte Differentiation of Mice Balb/C, Benzapyrene and 28 met the inclusion criteria.

Curcumin reduced the hepatocyte proliferation index in experimental animals exposed to BaP and increased the hepatocyte apoptosis index in experimental animals exposed to BaP. It reduced the N/C ratio of hepatocytes in experimental animals exposed to BaP.

Conclusion: Administration of curcumin in the diet during the initiation and post-initiation periods can inhibit the increase in PCNA expression, increase apoptosis, and improve hepatocyte differentiation patterns exposed to benzopyrene and curcumin

Keywords: Curcumin, proliferation, apoptosis, hepatocyte differentiation mice balb/C, benzapyrene, public health.

INTRODUCTION

Neoplasms (tumors), especially those that are malignant, are associated with high mortality and treatment is currently unsatisfactory. Mortality from cancer in Indonesia ranks 6th. WHO estimates the incidence of cancer is 180 per 100,000 population.¹ Hepatocellular Cell Carcinoma (HCC) is one of the most common internal organ neoplasms in humans.^{2,3} An increase in pollutants increases exposure to carcinogenic substances so that they can increase the frequency of cancer.¹

One of the toxic materials produced due to industrial processes is benzapyrene (BaP). It is a carcinogen, containing both an initiator and a promoter for tumors.⁴ One of the important organs for detoxification of toxic materials that enter the body due to environmental pollution is the liver. This can result in liver cell damage, which can lead to excessive cell proliferation, resulting in liver tumors or cancer.

Tumor development is affected by the balance between proliferation, apoptosis and differentiation.⁵ This can be assessed by the biological parameters of tumor development, among others through the assessment of changes in proliferation, apoptosis, and differentiation. Increased proliferation indicates an increase in tumor activity. A decrease in apoptosis indicates a local failure in the mechanism against cancer development.⁶ Changes in cell differentiation towards abnormal patterns indicate

changes in cells towards malignancy.⁷

Efficacy of the Curcuma species (a compatriot of turmeric) has been of interest. Plants of this class are known to be useful in traditional medicine against various diseases of the liver. Recent research has found that the active ingredient of various Curcuma species is curcumin. Curcumin (diferuloylmethane) is a yellow pigment that is widely obtained from the isolation of Curcuma species, Zingiberaceae.⁸ Curcumin is a polyphenolic compound with a beta-diketone moiety.⁹ Curcumin has activity as an anti-cancer, and until now research on this matter is still being developed.^{3,8,10-15} The purpose of this study was assess effects of Curcumin on the proliferation, apoptosis and differentiation of mice balb/C hepatocytes exposed to BaP.

METHODOLOGY

A literature search was carried out systematically through the PubMed, NCBI, Google Scholar databases using keywords, “Curcumin, proliferation, apoptosis and hepatocyte differentiation of Mice Balb/C, Benzapyrene” (Fig. 1). The articles obtained were first selected by setting several inclusion criteria including journals are not paid/free articles, research results focus on “Curcumin, proliferation, apoptosis and hepatocyte differentiation of Mice Balb/C, Benzapyrene”. Articles

that did not meet the inclusion criteria were excluded.

Statistical Analysis: SPSS version 21 was used for data analysis.

RESULTS

We obtained 550 articles for Curcumin, proliferation, apoptosis and hepatocyte differentiation of Mice Balb/C, Benzapyrene. All articles were re-selected based on inclusion criteria and exclusion and 28 articles that met the inclusion criteria were analysed.

Curcumin reduced the hepatocyte proliferation index in experimental animals exposed to BaP (Fig. 2). Curcumin increased the hepatocyte apoptosis index in experimental animals exposed to BaP (Fig. 3). Curcumin reduced the N/C ratio of hepatocytes in experimental animals exposed to BaP (Fig. 4).

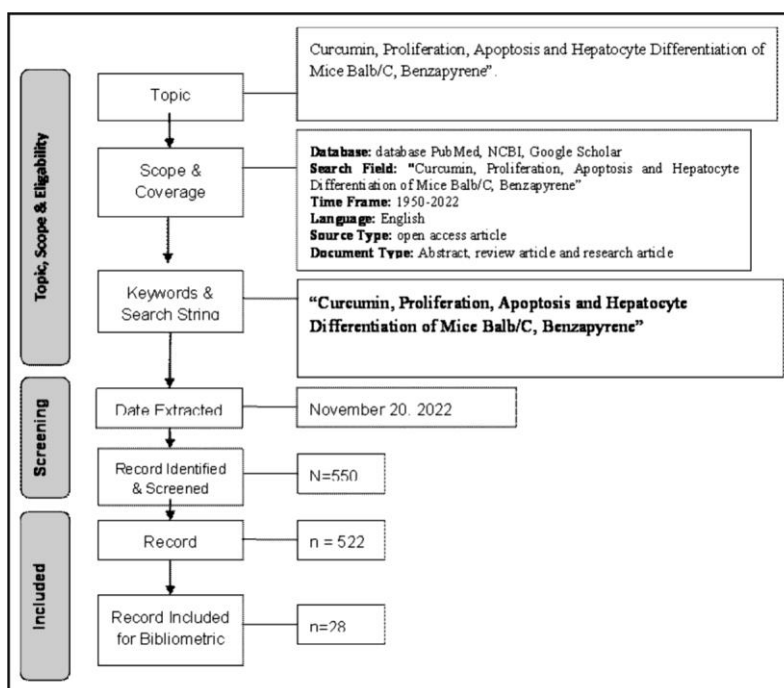


Fig. 1: Flow diagram of the search strategy.

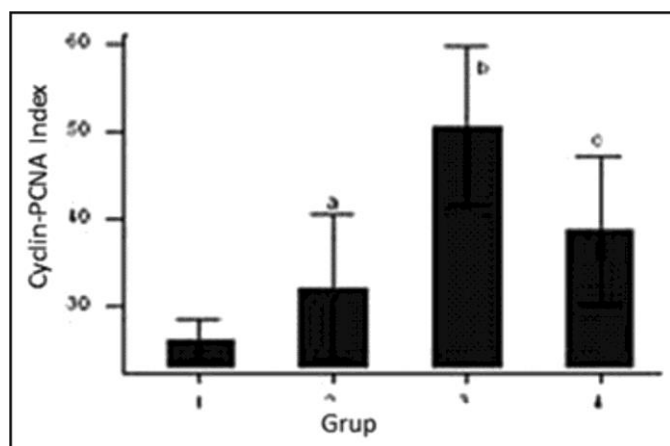


Fig. 2: Cyclin-PCNA index of hepatocytes in the 4 animal groups.

DISCUSSION

A study by Chuang et al,³ showed that administration of curcumin could return PCNA levels towards normal. They used immunohistochemistry and Western blotting method. The action of BaP in causing carcinogenesis is through mutations that occur due to guanine read as thymine (transversion).¹⁶ However, according to Halliwell et al, mutations in BaP are not only due to bonding covalent between the ultimate carcinogen and guanine, but also due to the formation of O₂ – radicals due to oxidation of BaP metabolites.¹⁷

Studies by Mahmoud et al¹⁰ and Kawamori et al¹³ further strengthens the evidence that curcumin may work in the same way as an anti-cancer. This was

demonstrated by an increase in apoptotic cells in mice injected with BaP, and this could be seen by HE is staining.

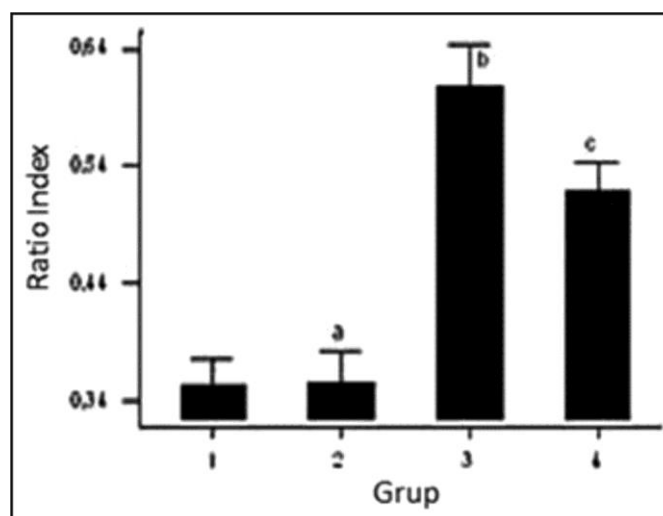


Fig. 3: Apoptotic index of hepatocytes in the 4 experimental animal groups.

Banjerdpongchai et al¹⁸ and Leu et al,⁹ reported that curcumin exhibited both antioxidant and pro-oxidant effects and at low doses, curcumin plays a role in free radical scavengers and electron or hydrogen donation, and this is what the protective effect of curcumin. While the pro-oxidant effect of curcumin can occur due to the presence of Cu (II) ions, in the presence of these ions, curcumin can cause the formation of reactive oxygen

species (ROS), especially hydroxyl radicals. This can happen because the structure of curcumin contains diferuloylmethane as a major composition and several minor derivatives, for example *monomethoxycurcumin*, *demethoxy-curcumin*, dan *bisdemethoxycurcumin*.

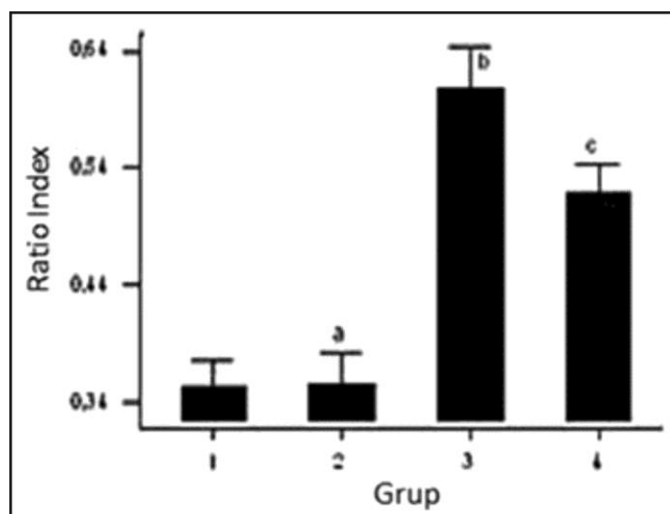


Fig.4: N/C Ratio of hepatocytes in the 4 experimental animal groups.

In the theory put forward by Halliwell et al,¹⁶ stated that in the body, BaP is converted into 7,8-diol-9,10-epoxide (ultimate carcinogen) by the enzyme cytochrome P-450, and then binds to guanine in DNA, causing damage to DNA. Peroxidase activity of the synthesis of prostaglandins, myeloperoxidase, and lactoperoxidase also converts BaP to 6-hydroxybenzpyrene, which is then oxidized so it becomes a quinone mixture by producing an O₂ – radical which then gets more cause DNA damage. DNA damage is caused by a covalent bond between the ultimate carcinogen or ROS and DNA. The covalent bonds damage the structure of DNA, so DNA replication is disrupted. If DNA damage occurs in the p53 tumor suppressor gene, it causes a p53 mutant, in accordance with previous studies which revealed that normally when there is DNA damage, normal p53 (wild type) will play a role in inhibiting proliferation, and encouraging DNA repair or apoptosis.^{5,17,19-21}

This causes a malfunction of p53.²¹ If the mutation occurs in the proto-oncogene, as stated by Sukardja,¹ it will cause changes in proto-oncogenes to become oncogenes which in turn code for the manufacture of peptides that are growth. In addition, the activity of several signal transduction proteins is also altered by ROS, namely tyrosine phosphatase, mitogen-activated protein kinase, NF-κB, and AP-1, where the effects of oxidation by ROS result in increased transcription and

are mitogenic.⁵

Curcumin's chemopreventive action against BaP is by activity ability extensive metabolic, cellular, and molecular curcumin. Leu et al, explained that curcumin worked as a substitute for a carcinogen (in this study it was BaP) to become ligand for Aryl Hydrocarbon Receptor (AHR), which is a receptor for detoxification enzymes, or even works to inhibit various cytochrome P450 isoenzymes, so that BaP as a pro-carcinogen is not converted into the ultimate carcinogen.⁹

Curcumin also acts as a free radical scavenger and increases hepatic glutathione S-transferase (GST) expression.^{8,9,22} This causes a bottleneck on DNA damage due to free radicals formed due to the oxidation of 6-hydroxybenzpyrene, one of the BaP metabolites. Another point of action of curcumin is on inhibition of DNA and RNA synthesis which results in inhibition of proliferation.¹⁴

Several other studies have explained that in terms of anti-proliferative effects, curcumin also suppresses c-Jun expression through inhibition of c-Jun N-Terminal Kinase (JNK), and suppresses c-fos expression through inhibition of extracellular signal-regulated protein kinase (ERK) so that it has an inhibitory effect on Activator Protein-1 (AP-1) activity, which results in inhibiting the activity of the enzyme Ornithine decarboxylase (ODC) and reducing ODC mRNA levels.^{8,9,15}

The theory put forward by several researchers that inhibition of AP-1 and NF-κB also causes inhibition of enzyme activity iNOS and inhibition of gene transcription and COX-2 enzyme activity.^{9,13} Curcumin also plays a role in inhibiting the expression of the oncoprotein k-catenin, a component of the adherent junction in cells intestinal epithelium and plays an important role in intercellular communication and cell migration.¹¹ Curcumin also causes inhibition of various other proteins involved in proliferation, including Protein Kinase C (PKC), PCNA, p21, CDC2, and epidermal growth factor. receptor (EGFR) Tyrosine Kinase (including p185neu).

Inhibition of PKC and protein tyrosine kinase causes inhibition of transcription activation of the Early Growth Response Gene Product (Egr-1).^{3,9,12} Curcumin causes an increase in apoptosis in various ways, including by increasing the formation of reactive oxygen species, especially hydroxyl radicals, as previously described.¹⁸ Oxidative stress due to the ROS that is formed then causes the release of cytochrome c from mitochondria, which further causes pro-caspase 3 activation and DNA fragmentation.

CONCLUSION

Administration of curcumin in the diet during the initiation and post initiation periods can inhibit the increase in PCNA expression, increased apoptosis, and improved hepatocyte differentiation patterns exposed to benzapyrene and curcumin. Need further research on other animals for future research.

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REFERENCES

1. Sukardja IDE. 2nd edition of Clinical Oncology. Airlangga University Press. Surabaya. 2000.
2. Grisham JW. Interspecies comparison of liver carcinogenesis: implications of cancer risk assessment. *Carcinogenesis* 1996;18:59-81.
3. Chuang SE, Cheng AL, Lin JK, Kuo ML. Inhibition by Curcumin of diethylnitrosamine-induced hepatic hyperplasia, inflammation, cellular gene product and cell-cycle related protein in rats. *Food Chem Toxicol* 2000;38:991-5.
4. Wang Y. 1997. Public Health Goals for Benzo(a)pyrene in Drinking Water. (http://www.oehha.ca.gov/water/phg/pdf/bap_c.pdf).
5. King RJB. Cancer Biology. Prentice Hall Pearson Education. New York. 2000.
6. Lyng H, Sundfør K, Tropé C, Rofstad EK. Disease control of uterine cervical cancer: relationships to tumor oxygen tension, vascular density, cell density, and frequency of mitosis and apoptosis measured before treatment and during radiotherapy. *Clin Cancer Res* 2000;6:1104-12.
7. Damjanov I. Histopathology. A Color Atlas and Textbook. Williams and Wilkins. 1996.
8. Lin JK, Lin-Shiau SY. Mechanisms of cancer chemoprevention by curcumin. *Proceedings of the National Science Council, Republic of China. Life Sci* 2001;25:59-66.
9. Leu TH, Maa MC. The molecular mechanisms for the antitumorigenic effect of curcumin. *Curr Med Chem Anti-Cancer Agent* 2002;2:357-70.
10. Perkins S, Verschoyle RD, Hill K, Parveen I, Threadgill MD, Sharma RA, et al. Chemopreventive efficacy and pharmacokinetics of curcumin in the min/+ mouse, a model of familial adenomatous polyposis. *Can Epidemiol Biom Prev* 2002;11:535-40.
11. Hong RL, Spohn WH, Hung MC. Curcumin inhibits tyrosine kinase activity of p185 neu and also depletes p185 neu. *Clin Can Res* 1999;5:1884-91.
12. Kawamori T, Lubet R, Steele VE, Kelloff GJ, Kaskey RB, Rao CV, et al. Chemopreventive effect of curcumin, a naturally occurring anti-inflammatory agent, during the promotion/progression stages of colon cancer. *Can Res* 1999;59:597-601.
13. Zhang F, Altorki NK, Mestre JR, Subbaramaiah K, Dannenberg AJ. Curcumin inhibits cyclooxygenase-2 transcription in bile acid-and phorbol ester-treated human gastrointestinal epithelial cells. *Carcinogenesis* 1999;20:445-51.
14. Huang MT. Inhibitory effects of topical application of low doses of curcumin on TPA-induced tumor promotion and oxidized DNA bases in mouse epidermis. *Carcinogenesis* 1997;18:83-8.
15. Lu YP, Chang RL, Lou YR, Huang MT, Newmark HL, Reuhl KR, et al. Effect of curcumin on 12-O-tetradecanoylphorbol-13-acetate-and ultraviolet B light-induced expression of c-Jun and c-Fos in JB6 cells and in mouse epidermis. *Carcinogenesis* 1994;15:2363-70.
16. Halliwell B, Gutteridge JMC. Free Radicals in Biology and Medicine, 3rd ed. Oxford University Press 1998.
17. Tchou-Wong KM, Jiang Y, Yee H, LaRosa J, Lee TC, Pellicer A, et al. Lung-specific expression of dominant-negative mutant p53 in transgenic mice increases spontaneous and benzo (a) pyrene-induced lung cancer. *Am J Resp Cell Mol Biol* 2002;27:186-93.
18. Banjerdpongchai R, Suttajit M, Kongtawelert P. Effect of curcumin on HL60 cell apoptosis induced by doxorubicin. *Chiang Mai Med Bull* 2002;41:59-66.
19. Yoon JH, Smith LE, Feng Z, Tang MS, Lee CS, Pfeifer GP. Methylated CpG dinucleotides are the preferential targets for G-to-T transversion mutations induced by benzo [a] pyrene diol epoxide in mammalian cells: similarities with the p53 mutation spectrum in smoking-associated lung cancers. *Can Res* 2001;61:7110-7.
20. Smith LE, Denissenko MF, Bennett WP, Li H, Amin S, Tang MS, et al. Targeting of lung cancer mutational hotspots by polycyclic aromatic hydrocarbons. *J Nat Can Inst* 2000;92:803-11.
21. Denissenko MF, Pao A, Tang MS, Pfeifer GP. Preferential formation of benzo [a] pyrene adducts at lung cancer mutational hotspots in P53. *Science* 1996;274(430-2).
22. Balasubramanyam M, Koteswari AA, Kumar RS, Monickaraj SF, Maheswari JU, Mohan V. Curcumin-induced inhibition of cellular reactive oxygen species generation: novel therapeutic implications. *J Biosci* 2003;28:715-21.

Evaluating physical therapy interventions for pediatric developmental disorders: Enhancing motor skill

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Objective: To evaluate the efficacy of specific physical therapy interventions, including Metaverse Physical Therapy, Nintendo Wii-integrated therapy, Whole-Body Vibration training, Segmental trunk and head control training, Ride-on car training, swimming programs, structured bimanual skill training, and running interventions in enhancing motor skills in children with pediatric developmental disorders.

Methodology: A systematic review of randomized controlled trials (RCTs) and longitudinal studies published from 2013 to 2023 was conducted. Studies that compared the effects of innovative physical therapy interventions such as metaverse physical therapy, virtual reality-enhanced treatments, and Nintendo Wii-integrated therapy, and traditional physical therapies on children with developmental disorders were included. Primary outcomes assessed included improvements in motor skills, cognitive functions, and social interactions.

Results: The review identified significant

improvements in motor function across various interventions. Innovations like metaverse physical therapy and virtual reality-enhanced treatments showed additional benefits in engagement and motivation. While all interventions generally improved motor skills, those incorporating advanced technologies and integrative approaches also positively impacted cognitive and social development, although to varying degrees.

Conclusion: Physical therapy, particularly when integrating new technologies and holistic approaches, is crucial for improving overall development in children with developmental disorders. The review highlights the need for personalized, multifaceted therapy plans that address not only physical but also cognitive and social needs to optimize outcomes.

Keywords: Pediatric developmental disorders, physical therapy, motor skill, specific intervention, training.

INTRODUCTION

Pediatric developmental disorders affect approximately 15% of children globally, presenting significant challenges in motor, cognitive, and social development. These disorders, which include conditions such as cerebral palsy, Down syndrome, and autism spectrum disorders, significantly impact the quality of life and functional capabilities of affected children. Pediatric developmental disorders encompass a broad spectrum of conditions that manifest in early childhood and can significantly impact various aspects of development, including motor, cognitive, social, and emotional skills.¹ These may include cerebral palsy, Down syndrome, autism spectrum disorders, and various genetic and neurological conditions. Globally, the prevalence of these disorders is substantial, affecting millions of children and their families, and poses considerable challenges to health systems and societal structures.²

Motor skills are fundamental to a child's ability to explore the world and interact with their environment. These skills are often significantly compromised in children with developmental disorders.³ For instance,

children with cerebral palsy may experience muscle spasticity, weakness, and coordination problems,⁴ while those with Down syndrome often face hypotonia and joint laxity, impacting their motor skill acquisition.⁵ The delay or impairment in motor skills can restrict participation in social and educational activities, limit independence, and reduce quality of life. Furthermore, impaired motor skills can lead to secondary health problems, such as contractures, deformities, and pain, exacerbating the child's condition and the family's challenges.³

Physical therapy is integral to managing these disorders, particularly in the optimization of motor function and general physical health. Current approaches in physical therapy are diverse, often incorporating traditional techniques with innovative technologies and methodologies. Techniques such as neurodevelopmental treatment, sensory integration therapy, and motor learning strategies are commonly used.⁶ Additionally, newer modalities such as robotic-assisted therapy and virtual reality are becoming increasingly prevalent, offering engaging and effective ways to enhance motor

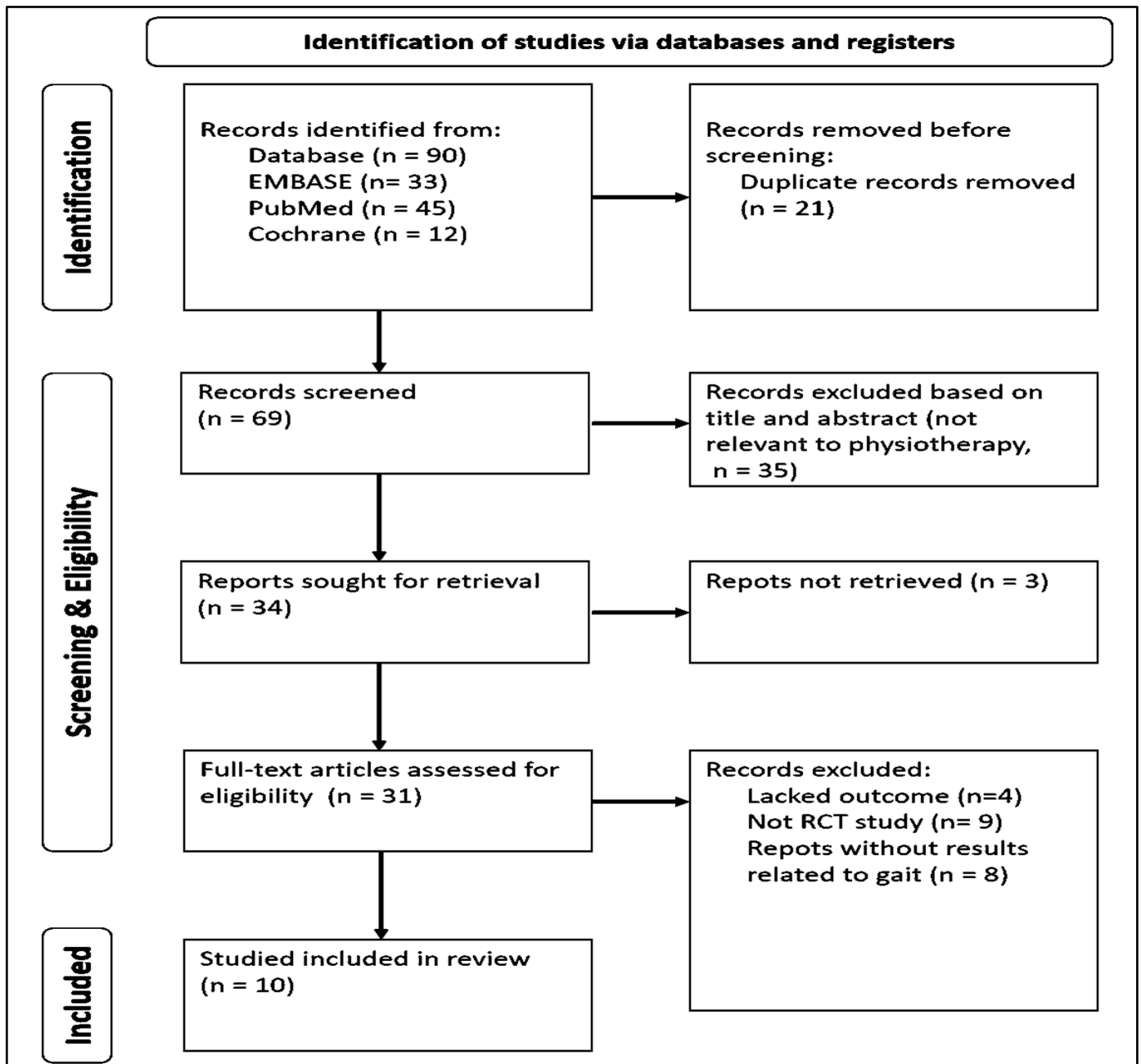


Fig. 1: PRISMA diagram showing the summary of the search process.

learning and rehabilitation.⁷

By improving motor skills, physical therapy not only enhances the functional capabilities of these children but also significantly contributes to their overall development and integration into society. This review aims to evaluate the efficacy of various physical therapy interventions in improving motor skills, cognitive functions, and social interactions in children with developmental disorders.

METHODOLOGY

The literature search was conducted using PubMed, Cochrane Library, and Embase, covering publications

from 2013 to 2023. Specific search terms included 'pediatric', 'physical therapy', and 'motor skills', combined using Boolean operators ('AND', 'OR') to refine results. For example, the search query "pediatric" AND "physical therapy" AND "motor skills" was used to identify relevant studies. This strategy retrieved studies that specifically addressed the intersection of physical therapy and motor skill enhancement in children with developmental disorders.

To maintain a high standard of evidence, only RCTs were included in the review. This selection criterion was imposed to ensure that the findings are based on the

highest level of evidence available, minimizing biases and enhancing the reliability of the conclusions. Studies not directly related to physical therapy interventions were rigorously excluded to maintain the focus and relevance of the review. The criteria for including studies in this review were as follows: 1) the study had to be a randomized controlled trial (RCT) to ensure high-quality evidence; 2) the study population included children aged 2 to 18 years with developmental disorders such as cerebral palsy, and Down syndrome; 3) the interventions studied were specific physical therapy techniques, including Metaverse Physical Therapy, Nintendo Wii-integrated therapy, Whole-Body Vibration training, Segmental trunk and head control training, Ride-on car training, swimming programs, structured bimanual skill training, and running interventions; and 4) the primary outcomes reported included improvements in motor skills, cognitive functions, and social interactions, with a specific focus on gait.

To ensure clarity and consistency in the analysis, only studies published in English were selected, allowing for a comprehensive evaluation of the literature without the potential inconsistencies arising from translation errors. To ensure the selection process was unbiased and reliable, three independent peer reviewers conducted the entire procedure. Any discrepancies that arose were addressed through collaborative discussions, and if needed, a fourth subject-matter expert was consulted for resolution. The process of selecting and classifying relevant studies was rigorously conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Fig. 1).

RESULTS

This systematic review identified 90 records across three databases (33 from EMBASE, 45 from PubMed, and 12 from Cochrane). From these, 21 duplicate records were removed, leaving 69 for screening. Upon review of titles and abstracts, 35 records were excluded for not being relevant to physiotherapy, narrowing the field to 34 records. After attempting to retrieve these reports, 3 were inaccessible. This led to 31 full-text articles being assessed for eligibility, of which 21 were further excluded for various reasons.

The relevant outcomes specified in the inclusion criteria were improvements in motor skills, cognitive functions, and social interactions. Studies that did not report on these primary outcomes were excluded (4 studies). Nine was not RCT studies, and 8 were missing results related to gait. Consequently, 10 studies met all criteria and were included in the review (Table 1). The outcomes of the included studies were categorized into three main areas: motor skills, cognitive development, and social

interactions. Each study's results were consistently reported under these categories to facilitate comparison and synthesis of findings.

Recent studies have evaluated various physical therapy interventions, revealing diverse benefits across different developmental and physical disabilities. For instance, START-Play therapy was shown to enhance cognitive development through motor-based problem-solving in infants.⁸ Metaverse Physical Therapy (MPT) improved gross motor and cardiopulmonary functions and reduced COVID-19 risk, though without affecting daily function or quality of life.⁹ The integration of Nintendo Wii into home-based therapy for children with cerebral palsy provided motor skill improvements and reduced parental stress.¹⁰ Whole-body vibration training combined with traditional physiotherapy significantly enhanced walking ability and postural control in children with hemiparetic cerebral palsy without altering muscle strength ratios.¹¹ Meanwhile, segmental training improved short-term control of head and trunk movements but did not surpass usual care in enhancing overall motor function.¹² Ride-on car training significantly boosted mobility and social function, particularly when conducted in a standing posture.¹³ A swimming program for youth with cerebral palsy sustained improvements in walking and swimming skills over time, without increasing fatigue or pain.¹⁴ Structured bimanual skill training promoted motor cortex plasticity and improved motor outcomes.¹⁵ Running interventions significantly enhanced running capabilities and school participation for children with cerebral palsy.¹⁶ Lastly, both core stability exercises and treadmill training were effective in improving balance in children with Down Syndrome.¹⁷

DISCUSSION

Physical therapy plays a pivotal role in managing pediatric developmental disorders by addressing motor, cognitive, and social impairments. Improved motor skills enhance a child's ability to interact with their environment, leading to secondary cognitive and social benefits. Enhanced mobility fosters greater participation in social and educational activities, promoting overall development and integration into society.¹⁸

Firstly, physical therapy is crucial because it addresses the foundational motor impairments commonly associated with developmental disorders. These impairments include limitations in strength, range of motion, coordination, and balance. By improving these fundamental aspects, physical therapy facilitates greater independence in daily activities such as walking, sitting, or handling objects, which are essential for personal autonomy and quality of life.¹⁹

Secondly, the improvement in motor skills through

Table 1: Summary of the eligible articles.

Author	Diagnosis	Methodology	Outcome
1. Koziol et al. (2023) ⁸	Infants with motor delays	START-Play physical therapy	Early physical therapy combines developmental activities can improve cognitive development with motor delays through enhanced motor-based problem-solving.
2. Moon et al. (2023) ⁹	Cerebral palsy	Metaverse physical therapy (MPT)	MPT showed promise for improving gross motor and cardiopulmonary function, and reducing COVID-19 transmission risk in children with cerebral palsy, compared to conventional physical therapy.
3. Wang et al. (2021) ¹⁰	Cerebral palsy	Nintendo Wii + Constraint-induced therapy (CIT)	Integrating Nintendo Wii into home-based CIT for children with cerebral palsy offers similar improvements in motor skills and playfulness as conventional CIT.
4. Hegazy & Abdel-Aziem (2022) ¹¹	Hemiparetic cerebral palsy	Whole-body vibration (WBV) + physiotherapy	WBV exercises combined with traditional physiotherapy improved walking ability, postural control, and muscle strength.
5. Curtis et al. (2018) ¹²	Moderate-to-severe cerebral palsy	Segmental trunk and head control training	Segmental training did not outperform conventional physiotherapy in improving overall gross motor function although it did provide short-term improvements in head and trunk control.
6. Huang et al. (2023) ¹³	Children with motor delays	Ride-on car (ROC) training	ROC training enhanced mobility and goal attainment in children with motor delays, with training in a standing posture also significantly improving social function.
7. Declerck et al. (2016) ¹⁴	Cerebral palsy	Swimming intervention	A swimming program was enjoyable and effectively improved walking and swimming skills without increasing fatigue and pain, with benefits maintained after 20 weeks.
8. Friel et al. (2016) ¹⁵	Unilateral spastic cerebral palsy (USCP)	Skilled bimanual training	Structured bimanual skill training, as opposed to unstructured practice, enhances motor outcomes and induced greater motor cortex plasticity in children with unilateral spastic cerebral palsy.
9. Gibson et al. (2018) ¹⁶	Cerebral palsy	Running intervention	A 12-week running intervention significantly improves running ability and increases participation in school activities for children with cerebral palsy.
10. Alsakhawi & Elshafey (2019) ¹⁷	Down syndrome	Core stability exercises and treadmill training	Core stability exercises and treadmill training both effectively enhance balance in children with Down syndrome when combined with traditional physical therapy.

targeted physical interventions often leads to secondary benefits in cognitive and social domains. Enhanced motor ability allows children greater interaction with their environment, which is critical for cognitive development.²⁰ Furthermore, increased mobility can

improve social interactions, as children gain the physical capability to participate more fully in play and educational activities with peers, thereby enhancing their social inclusion and emotional well-being.²¹ Moreover, physical therapy is not a one-size-fits-all

approach. It requires a tailored strategy that considers the individual needs and goals of each child. This customization is vital because developmental disorders present with a spectrum of symptoms and severities, and what works for one child may not be effective for another. Physical therapists, therefore, must develop and adjust intervention plans based on ongoing assessments of each child's progress and challenges.²²

This systematic review underscores the varied and significant impacts of different physical therapy interventions on children with developmental disorders. Throughout the studies, it is evident that specific interventions like START-Play,⁸ Metaverse Physical Therapy,⁹ and Nintendo Wii integrated therapy not only address motor skills but also touch on cognitive and psychosocial dimensions,¹⁰ which are crucial for comprehensive pediatric care.

The evidence consistently shows that while traditional therapies remain beneficial,^{12,14-16} incorporating innovative approaches like metaverse physical therapy⁹ or using assistive technologies such as Nintendo Wii¹⁰ can lead to better engagement and outcomes. These interventions tend to offer more than just physical benefits; they enhance motivation and potentially reduce the psychological burden on caregivers as seen in the reduced parental stress in Wii-integrated therapies. Furthermore, interventions such as whole-body vibration training¹¹ and specialized running programs¹⁶ have shown promising results in not only enhancing motor function but also in improving participation in social and educational activities, which are critical for the holistic development of children with disabilities.

Despite these advances, the studies reviewed highlight a critical gap in accessibility and the need for personalized treatment plans. The variability in response to the interventions suggests that therapy needs to be highly tailored, taking into consideration the unique needs and potential of each child. The findings also suggest a need for ongoing innovation and research in physical therapy approaches, particularly in integrating new technologies that can be adapted for home use, thereby increasing accessibility and consistency of therapy delivery. Challenges in current research include accessibility issues and the variability in response to interventions, underscoring the need for personalized treatment plans. Future research should focus on developing accessible, home-based technologies and conducting longitudinal studies to evaluate long-term outcomes of physical therapy interventions.

CONCLUSION

This review demonstrates the efficacy of both traditional and innovative physical therapy interventions in

enhancing motor skills, cognitive functions, and social interactions in children with developmental disorders. A multidimensional approach, integrating advanced technologies and personalized therapy plans, is essential for optimizing outcomes and transforming pediatric care.

Author Contributions:

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REFERENCES

1. Lipkin PH, Macias MM. Council on children with disabilities, section on developmental and behavioral pediatrics. Promoting Optimal Development: Identifying Infants and Young Children with Developmental Disorders Through Developmental Surveillance and Screening. *Pediatrics* 2020;145:e20193449.
2. Chang MC. Pediatric Physical Medicine and Rehabilitation. *Children (Basel)* 2022;9:954-8.
3. Dobell A, Pringle A, Faghy MA, Roscoe CMP. Fundamental Movement Skills and Accelerometer-Measured Physical Activity Levels during Early Childhood: A Systematic Review. *Children (Basel)*. 2020;7:224-9.
4. Bekteshi S, Monbaliu E, McIntyre S, Saloojee G, Hilberink SR, Tatishvili N, et al. Towards functional improvement of motor disorders associated with cerebral palsy. *Lancet Neurol* 2023;22:229-43.
5. Koo D, Pathak P, Moon J, Panday SB. Analysis of the relationship between muscular strength and joint stiffness in children with Down syndrome during drop landing. *Technol Health Care* 2022;30:383-90.
6. Dannemiller L, Mueller M, Leitner A, Iverson E, Kaplan SL. Physical Therapy Management of Children with Developmental Coordination Disorder: An Evidence-Based Clinical Practice Guideline from the Academy of Pediatric Physical Therapy of the American Physical Therapy Association. *Pediatr Phys Ther* 2020;32:278-313.
7. Olmos-Gómez R, Gómez-Conesa A, Calvo-Muñoz I, López-López JA. Effects of Robotic-Assisted Gait Training in Children and Adolescents with Cerebral Palsy: A Network Meta-Analysis. *J Clin Med* 2021;10:4908-11.
8. Koziol NA, Kretch KS, Harbourne RT, Lobo MA, McCoy SW, Molinini R, et al. START-Play Physical Therapy Intervention Indirectly Impacts Cognition Through Changes in Early Motor-Based Problem-Solving Skills. *Pediatr Phys Ther* 2023;35:293-302.
9. Moon I, An Y, Min S, Park C. Therapeutic Effects of Metaverse Rehabilitation for Cerebral Palsy: A Randomized Controlled Trial. *Int J Environ Res Public Health* 2023;20:1578-82.
10. Wang TN, Chen YL, Shieh JY, Chen HL. Commercial Exergaming in Home-Based Pediatric Constraint-Induced

- Therapy: A Randomized Trial. *OTJR* (Thorofare N J). 2021;41:90–100.
11. Hegazy RG, Abdel-Aziem AA. Effect of Whole-Body Vibration Exercise on Hamstrings-to-Quadriceps Ratio, Walking Performance, and Postural Control in Children with Hemiparetic Cerebral Palsy: A Randomized Controlled Trial. *J Manipulative Physiol Ther* 2022;45:660–70.
 12. Curtis DJ, Woollacott M, Bencke J, Lauridsen HB, Saavedra S, Bandholm T, et al. The functional effect of segmental trunk and head control training in moderate-to-severe cerebral palsy: A randomized controlled trial. *Dev Neurorehabil* 2018;21:91–100.
 13. Huang HH, Hsieh YH, Chang CH, Tsai WY, Huang CK, Chen CL. Ride-on car training using sitting and standing postures for mobility and socialization in young children with motor delays: a randomized controlled trial. *Disabil Rehabil* 2023;45:1453–60.
 14. Declerck M, Verheul M, Daly D, Sanders R. Benefits and Enjoyment of a Swimming Intervention for Youth with Cerebral Palsy: An RCT Study. *Pediatr Phys Ther* 2016;28:162–9.
 15. Friel KM, Kuo HC, Fuller J, Ferre CL, Brandão M, Carmel JB, et al. Skilled Bimanual Training Drives Motor Cortex Plasticity in Children with Unilateral Cerebral Palsy. *Neurorehabil Neural Repair* 2016;30:834–44.
 16. Gibson N, Chappell A, Blackmore AM, Morris S, Williams G, Bear N, et al. The effect of a running intervention on running ability and participation in children with cerebral palsy: a randomized controlled trial. *Disabil Rehabil* 2018;40:3041–9.
 17. Alsakhawi RS, Elshafey MA. Effect of Core Stability Exercises and Treadmill Training on Balance in Children with Down Syndrome: Randomized Controlled Trial. *Adv Ther* 2019;36:2364–73.
 18. Gonzalez NA, Sanivarapu RR, Osman U, Latha Kumar A, Sadagopan A, Mahmoud A, et al. Physical Therapy Interventions in Children with Cerebral Palsy: A Systematic Review. *Cureus* 2023;15:e43846.
 19. Patel DR, Neelakantan M, Pandher K, Merrick J. Cerebral palsy in children: a clinical overview. *Transl Pediatr* 2020;9:S125–35.
 20. Dusing SC, Harbourne RT, Lobo MA, Westcott-McCoy S, Bovaird JA, Kane AE, et al. A Physical Therapy Intervention to Advance Cognitive and Motor Skills: A Single Subject Study of a Young Child with Cerebral Palsy. *Pediatr Phys Ther* 2019;31:347–52.
 21. Bar-Haim S, Aviram R, Shkedy Rabani A, Amro A, Nammourah I, Al-Jarrah M, et al. Effects of Exercise Interventions on Habitual Physical Activity and Sedentary Behavior in Adolescents with Cerebral Palsy. *Pediatr Exerc Sci* 2019;31:416–24.
 22. Faccioli S, Pagliano E, Ferrari A, Maghini C, Siani MF, Sgherri G, et al. Evidence-based management and motor rehabilitation of cerebral palsy children and adolescents: a systematic review. *Front Neurol* 2023;14:1171224.

Social anxiety disorder in Asian adolescents and parenting: A systematic review

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Objective: To systematically review the effect of parenting styles, self esteem, quality of life, emotional intelligence, and brain activity on social anxiety disorder (SAD) in adolescents, specifically in Asian countries.

Methodology: Studies included were based on the age of the participants which falls between the range of 6-20 years. These were related to SAD in adolescents, associated factors including parenting style, self esteem, quality of life, emotional intelligence and brain activity. All these were in the English language and published between 2012 to 2022. Data were taken from three research gates; Google scholar, PubMed and Science Direct. All studies were from Pakistan, India, Saudi Arabia and China.

Results: SAD was directly associated with authoritarian parenting style, interbrain synchrony

between parents and adolescents, low self esteem, challenged quality of life, weaker emotional intelligence, and higher activity in the amygdala of the brain.

Conclusion: SAD is a common phenomenon in patriarchal societies. In these societies authoritarian parenting is commonly exercised that results in serious challenges like low self esteem, weak emotional intelligence and low quality of life of the individual. It also affects brain functioning as the activity in the amygdala increases and gamma interbrain synchrony also decreases. All of these factors affect the life of adolescents experiencing SAD in different circumstances.

Keywords: SAD, social phobia, adolescence, life quality, parenting, self-esteem, amygdala.

INTRODUCTION

SAD disorder or social phobia is a fear of being judged in social situations. This fear is an emotion that is faced by the individual while dealing with social situations. Emotions in the brain are associated with amygdala working in the brain. Thus, when SAD is experienced the amygdala in the brain comes into action.¹ In a study, there was noted a significantly greater activity in amygdala, rostral, dorsomedial and lateral frontal and parietal cortices of the brain using MRI.²

A lifetime prevalence of SAD disorder of up to 12% has been reported in the United States, and 1-year prevalence rate of 0.8% was noted in Europe. The prevalence in adolescents in Asian countries are; China 0.2%,³ India 12.8%,⁴ and Pakistan 22.5%,⁵ In meta-analysis, 28 out of 32 studies suggested that Asian heritage had higher self-reported SAD as compared to European heritage.⁶ One of the possible explanations is that Asian individuals belong to collectivistic culture and are more likely to experience embarrassment and anxiety.⁷

SAD is affected by different elements such as parenting style, self esteem, quality of life, wellbeing, emotional intelligence, and emotions. It is also related to the brain's anatomy and functioning.⁸ Connecting SAD to emotions and emotional intelligence, we can state that anxiety itself is an emotion that is fear whereas emotional intelligence

deals with the management and understanding of one's own emotions that is fear.⁹ An authoritarian parenting style is involved in development of SAD in the individual,¹⁰ which involves strict rules and punishments.¹¹ Mindful parenting that includes the sense of freedom, acceptance and openness brings a positive attitude in parent child relationships.¹²

Mostly in male dominant societies like India and Pakistan use authoritarian parenting styles. Low self esteem is also a result of authoritarian parenting that leads towards maladaptive behaviours and development of SAD.¹³ The factors that affect SAD in children due to parenting is caused by familial attitudes, modelling of negative beliefs and thoughts that creates the perception that the society is not a safe place, and over personalising others' opinions to oneself. Similarly, interbrain synchrony between parent and child is the child's first social interaction in this world.¹⁴ Thus, SAD is related to interbrain synchrony between the parent and the individual.

The significance of conducting this review was to explore different factors that are associated specifically with SAD among adolescents in Asian culture. It will help researchers in future to streamline exploratory and therapeutic protocol keeping the needs of Asian cultures aligned in order to establish understanding of

symptomatology of SAD and its manifestation in indigenous context.

METHODOLOGY

According to the recommendations by PRISMA suggested for reporting, this systematic review was conducted from October 2022 to March 2023 (Fig.). It included 50 articles in English from 2012 to 2022. The articles were systematically sorted based on inclusion criteria searched and reported the details including: author, title, year, demographics, design, analysis, method, variables, sample, outcome, and references. Several search engines were employed; Science Direct, Google Scholar, research gate and PubMed. Google Scholar (6/10) was used for 60% of the articles. Search phrases included Pakistan, India, and China. It assisted in providing more relevant papers for scrutinizing research and its evaluation. Research conducted in peripheral countries were also represented in the pool of articles.

Article searches were done using keywords: SAD, social phobia, parenting, self-esteem, neglect. Adolescence, SAD, parenting, quality of life, amygdala, and self-esteem were the significant words. The articles that, based on demographics and other data, did not fulfil our inclusion criterion were eliminated. There were 50 articles in total that were downloaded from databases. There was one duplicate article, which was removed, leaving 49 items to analyze. A total of 40 articles from the systematic review were eliminated. After eliminating

them, 13 papers were sorted for systematic review, which met inclusion criteria.

RESULTS

The majority of the adolescents in all the studies ranged in age from 11 to 18. One study's age sample ranged from 6 to 11 years. In this review, 50% of the articles came

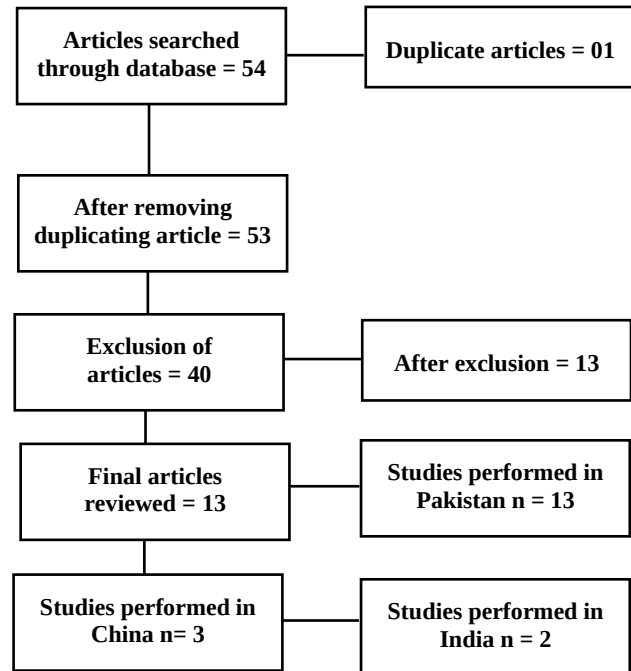


Fig. 1: PRISMA model for review.

Table 1: Methodological characteristics and findings of included studies.

Author & region	Year	Study design	Sample	Findings
Mehmooda et al ¹⁵ (Pakistan)	2017	Correlational	N=300	Self-esteem predicts social connectedness and social anxiety. Self-esteem is a negative predictor of self-esteem whereas, positively predicts social connectedness.
Parvez & Saima ¹⁶ (Pakistan)	2013	Correlational	N=200	There are psychological correlates of social anxiety Parenting styles are a predominant reason for social anxiety
Saleh et al ¹⁷ (Saudia Arabia)	2014	Cross-sectional	N=564	Culture influences the nature of social anxiety in these adolescents. Adolescents with social anxiety have lower score on quality of life.
Inam et al ¹⁸ (Pakistan)	2014	Cross-section	N=130	Emotional intelligence has a relationship with social anxiety. Adolescents that have emotional intelligence are less socially anxious and this affects the teenagers' social skills in both genders.

Farooq et al ¹⁹ (Pakistan)	2017	Cross-section	N=450	Social anxiety affects the quality of life. Adolescents in Pakistan have social anxiety in school. Social anxiety can be managed with the use of group therapies.
Mishra and Kiran ²⁰ (India)	2018	Independent group design	N=120	Parenting styles are associated with social anxiety. Social anxiety is caused by authoritarian and uninvolved parenting.
Sandhu and Sharma ²¹ (India)	2015	Exploratory	N=227	Social anxiety and social withdrawal are caused by neglect, rejection, and authoritarian, unreasonable parenting practices.
Rana et al ²² (Pakistan)	2013	Independent group design	N=200	Adolescents are more prone to social anxiety when their parents have authoritarian parenting styles and when their fathers are uninvolved in their lives.
Nasreen et al ²³ Pakistan	2012	Correlational	N=210	Social anxiety and self-esteem do not differ much by gender. There are not much gender differences in social anxiety
Ahmad et al ²⁴ (Pakistan)	2013	Cross-section	N=210	A poor relationship exists between low self-esteem and social anxiety.
Chong-Wen et al ³ (China)	2022	Cross sectional	N=302	Adolescents and social anxiety have a bad link, whereas self-esteem and social anxiety have a good one.
Deng et al ¹⁴ (China)	2022	Mixed	N=192	Due to the varied degrees of anxiety among adolescents, there is a variation in how parents and children handle identical emotional situations. Results also revealed that emotional regulation is associated with social anxiety
Mao et al, ¹⁰ (China)	2020	Longitudinal		Orbito-frontal cortex play a role in social anxiety.

from Pakistan, with the remaining 30% from China and 20% from India.

Two out of ten were derived from Science Direct, accounting for 20%. The two were taken from PubMed and Research Gate. The research used a cross-sectional study design for 40% of the study, 20% of the research was done by 2 independent groups. The other two studies were correlational investigations, while the rest of 2 were longitudinal and exploratory studies. Results of these studies^{3,4,10,15-24} are shown in the Table 1.

DISCUSSION

The study aimed to unwrap several different factors contributing to SAD among adolescents in India, Pakistan, and China. The first factor was composite parenting behaviours, including parenting styles and dimensions, which influence a child's anxiety levels.²⁵

Another contributing factor was poor quality of life, which is related to social and economic factors in these countries.^{26,27}

Additionally, the study looked at neurological functioning and inter-brain synchrony, two traits that play a role in the development of SAD.⁷ According to these studies two other factors that are associated with SAD are emotional intelligence, and self-esteem. The researchers sought to determine whether these traits were associated with isolation and detachment behaviours among adolescents and whether they contributed to the prevalence of SAD. By uncovering these relationships and unique contributing factors, the study hoped to shed light on how to address SAD in adolescents in these three Countries (India, Pakistan and China).²⁸

The review also has limitations when it comes to the quality and reliability of the data used as many studies

relied on self-reported measures, which can be subject to biases and inaccuracies. Moreover, the review did not cover all possible factors that may contribute to mental health problems among adolescents, including social and environmental factors, which should be considered in future research. Additionally, there may be difficulties in the data presented due to variations in the way mental health problems are conceptualised, diagnosed, and treated across different countries and cultures.

While this review provides valuable insights into the prevalence and factors associated with mental health problems among adolescents in China, Pakistan, and India, it is important to acknowledge its limitations and exercise caution when generalising the findings to other cultures and countries. Further research using larger samples and comprehensive methodologies is needed to better understand the complex interplay of factors that contribute to mental health problems among adolescents.

CONCLUSION

In line with the review conclusions drawn, it is advised to disseminate the information among families that adopting considerate parenting practices can help adolescents keep their sense of self-worth, which may prevent them from experiencing SAD. Also, preventing the onset of SAD disorder and mental disease in children requires teaching parents and teachers about anxiety problems and enlisting their cooperation. A school-based group treatment programme is recommended to assist teenagers in overcoming their SAD.

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REFERENCES

- Kraus J, Frick A, Fischer H, Howner K, Fredrikson M, Furmark T. Amygdala reactivity and connectivity during social and non-social aversive stimulation in SAD disorder. *Psychiatry Research: Neuro Imag* 2018;280:56-61.
- Blair KS, Otero M, Teng C, Geraci M, Lewis E, Hollon N, et al. Learning from other people's fear: amygdala-based social reference learning in SAD disorder. *Psychol Med* 2016;46:2943-53.
- Chong-Wen W, Sha-Sha L, Xu E. Mediating effects of self-esteem on the relationship between mindful parenting and social anxiety level in Chinese adolescents. *Medicine* 2022 Dec 9;101(49):e32103.
- Shi QC, Zhang JM, Xu FZ, Phillips MR, Xu Y, Fu YL, et al. Epidemiological survey of mental illnesses in the people aged 15 and older in Zhejiang Province, China. *Chin J Prev Med* 2005;39:229-36.
- Mehtalia K, Vankar GK. SAD in adolescents. *Ind J Psych* 2004;46:221-8.
- Wong QJ, Chen J, Gregory B, Baillie AJ, Nagata T, Furukawa TA, et al. Measurement equivalence of the Social Interaction Anxiety Scale (SIAS) and Social Phobia Scale (SPS) across individuals with SAD disorder from Japanese and Australian sociocultural contexts. *J Affect Disord* 2019;243:165-74.
- Bano Z, Ahmed R, Riaz S. SAD in adolescents: Prevalence and morbidity. *Pak Armed Forces Med J* 2019;69:1057-60.
- Petrides KV, Furnham A. Trait emotional intelligence: Psychometric investigation with reference to established trait taxonomies. *Eur J Pers* 2001;15:425-48.
- Asbrand J, Hudson J, Schmitz J, Tuschen-Caffier B. Maternal parenting and child behaviour: An observational study of childhood SAD disorder. *Cogn Ther Res* 2017;41:562-75.
- Mao Y, Zuo XN, Ding C, Qiu J. OFC and its connectivity with amygdala as predictors for future social anxiety in adolescents. *Developmental Cognitive Neurosci* 2020;44:100804.
- Ilyas U, Khan SD. Role of Parenting and Psychosocial Correlates Contributing to Social Anxiety in Asian Adolescents: A Systematic Review. *Innovations Clin Neurosci* 2023;20(7-9):30-5.
- McLeod BD, Wood JJ, Weisz JR. Examining the association between parenting and childhood anxiety: A meta-analysis. *Clin Psychol Rev* 2007;27:155-72.
- Ilyas U, Dawood S. Social Anxiety, Shyness-Inhibition and Conceptualized Self: A Qualitative Investigation in Collectivistic Cultures. *Human Nature* 2024;5:143-51.
- Deng X, Chen X, Zhang L, Gao Q, Li X, An S. Adolescent SAD undermines adolescent-parent interbrain synchrony during emotional processing: A hyperscanning study. *Int J Clin Health Psychol* 2022; 22:100329.
- Fatima M, Niazi S, Ghayas S. Relationship between self-esteem and social anxiety: Role of social connectedness as a mediator. *Pak J Soc Clin Psychol* 2017; 15:12-7.
- Parvez S. Prevalence and psychological correlates of social anxiety disorder among university students in Peshawar. (Doctoral dissertation, University of Peshawar). Retrieved from Pakistan Research Repository (PRR). 2013.
- SALEHA A. Reading Social Changes in Japanese Literature around 1990-2010: Existential Anxiety in Self-Identity (Doctoral dissertation, Nanzan University, Japan.).
- Inam A, Khalil H, Tahir WB, Abiodullah M. Relationship

- of emotional intelligence with SAD and social competence of adolescents. *Nurture* 2014; 8:20-9.
19. Farooq SA, Muneeb A, Ajmal W, Tauni MA, Mahmood S, Qadri SK, et al. Quality of life perceptions in school-going adolescents with social anxiety. *J Childhood Developmental Disord* 2017;3(2):1-5.
20. Mishra PI, Kiran UV. Parenting style and social anxiety among adolescents. *Int J Appl Home Sci* 2018;5:117-23.
21. Sandhu GK, Sharma V. Social withdrawal and social anxiety in relation to stylistic parenting dimensions in the Indian cultural context. *Res Psychol Behav Sci* 2015;3:51-9.
22. Rana SA, Akhtar S, Tahir MA. Parenting styles and social anxiety among adolescents. *New Horizons* 2013;5:117-138.
23. Nasreen B, Zaeema R A, Amena Z A. Relationship of self-esteem and social anxiety: a comparative study between male and female adolescents. *Pak J Clin Psy* 2012;11:15-23
24. Ahmad ZR, Bano N, Ahmad R, Khanam SJ. Social anxiety in adolescents: Does self-esteem matter. *Asian J Soc Sci Humanities* 2013;2:91-8.
25. Chorpita BF, Barlow DH. The development of anxiety: The role of control in the early environment. *Neurotic Paradox* 2018; 2:227-64.
26. Lamborn SD, Mounts NS, Steinberg L, Dornbusch SM. Patterns of competence and adjustment among adolescents from authoritative, authoritarian, indulgent, and neglectful families. *Child Dev* 1991;62:1049-65.
27. Armsden GC, Greenberg MT. The inventory of parent and peer attachment: Individual differences and their relationship to psychological well-being in adolescence. *J Youth Adolesc* 1987;16:427-454.
28. Alkhathamia S, Kaviania H, Shorta E. Social anxiety among adolescents and its relation to quality of life. *Eur Proc Soc Behav Sci* 2014; 218:228.

Association of resilience with caregiver burden in caring for the elderly with stroke; a systematic review

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Objective: To review the construct of resilience and related variables in caregivers caring for older adults with stroke and factors influencing caregiver burden.

Methodology: The review included studies published between February 2009 and February 2024, using the Preferred Reporting Items for Systematic Reviews. The PubMed, Web of Science, Scopus, China Academic Journals, Wan Fang Data Knowledge Service Platform, China Science and Technology Journal Database databases were employed.

Results: In all 18 investigations, 14 quantitative and 2 qualitative were found. Resilience was linked to positive impacts on life satisfaction and emotional pain in these studies. Building robust coping skills can be

facilitated by social support and communication. The majority of the chosen papers employed convenience sampling. Semi-structured interviews were utilized to gather qualitative and quantitative data utilizing resilience-related elements and evaluation tools.

Conclusion: Encouraging caregivers to adopt a resilient coping style helps them feel less distressed about changes in their biopsychosocial and spiritual aspects that come with sickness. A resilient coping strategy can help the caregiver adjust while lowering their risk of stress and strain.

Keywords: Resilience, stroke, elderly, caregiver, care burden, systematic review.

INTRODUCTION

Stroke or cerebrovascular accident (CVA) is an acute disorder, which includes ischemic and hemorrhagic stroke, and causes damage to brain tissue as a result of abruptly rupturing blood vessels in the brain or obstructing blood arteries that prevent blood from entering the brain. It one of the seconding leading causes of death and third leading cause of disability.¹ Its incidence in the elderly is significantly higher than that the younger population.^{2,3}

Stroke not only affects the patient himself, but also places a heavy burden on his family. Elderly stroke patients are often accompanied by other chronic diseases and functional impairments.⁴ Therefore, the care of older stroke patients involves emotional and physical changes. Caregivers face risks associated with care needs that increase stress and undermine personal performance.

Resilience is a powerful social-psychological capacity that can reduce negative emotions during crises while enhancing adaptability, plays an important role in motivating caregivers to maintain mental health, participate in helping them take care of the anxiety and depression caused by stroke patients and ultimately improve their quality of life.^{5,6} By focusing on the cultural aspect, we can understand resilience more systematically.⁷

Despite the impact of diversity, resilience is a key

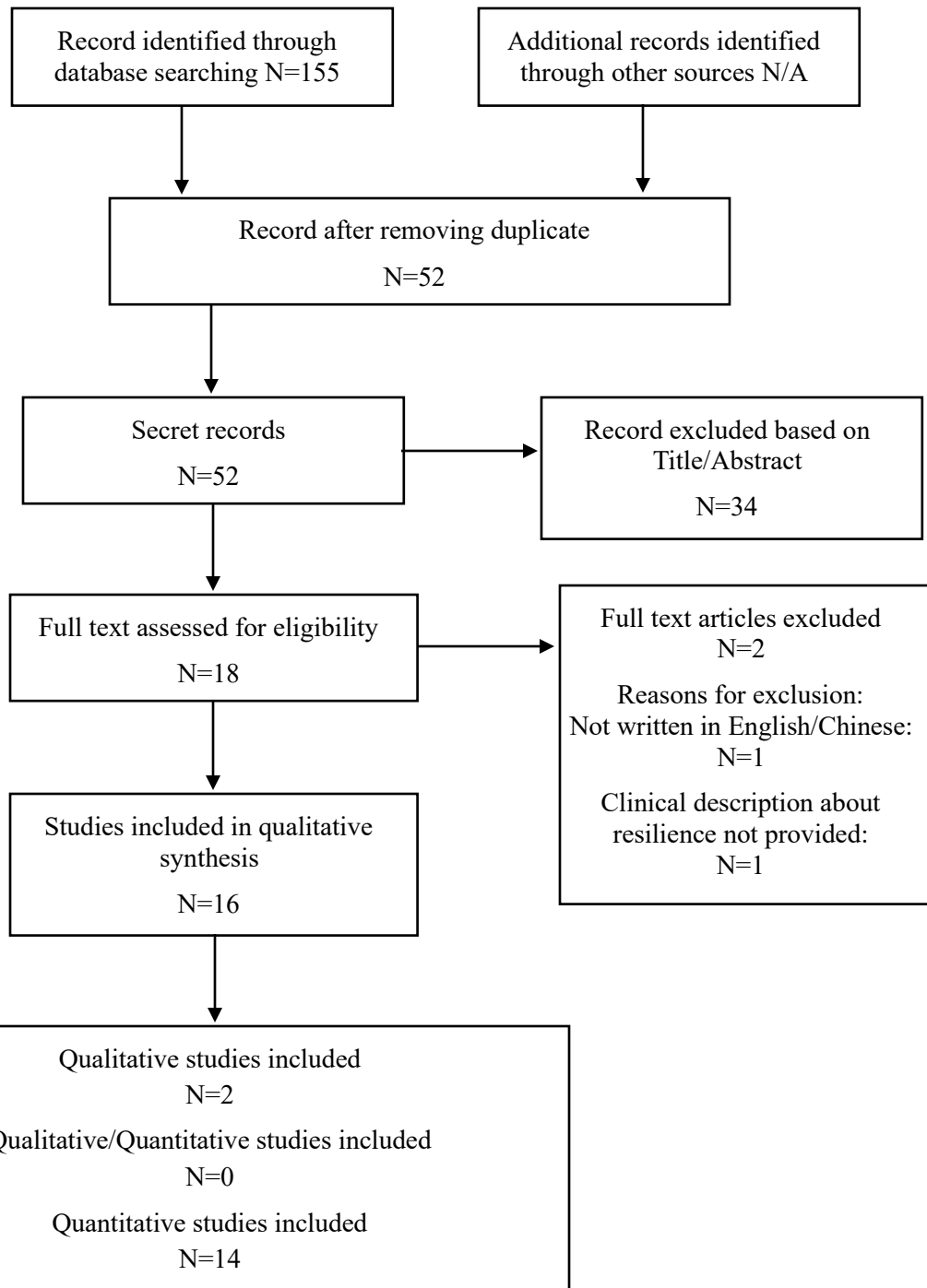
strength in helping caregivers overcome the difficulties of caring for stroke patients. However, using disparate findings as evidence-based knowledge to attempt to improve caregiver resilience is limited. There is also a lack of comprehensive research specifically targeting caregivers of stroke patients in Malaysia. The lack of in-depth research on the unique challenges faced by Malaysian caregivers creates a significant knowledge gap.

This paper aims to provide a thorough theoretical and practical basis for improving support for caregivers across Malaysia by analyzing the role of elasticity and its associated psychological factors in emotional distress and well-being.

METHODOLOGY

This systematic review used PRISMA statement for guidelines for published articles.

The PubMed, Web of Science, Scopus, China Academic Journals, Wan Fang Data Knowledge Service Platform, China Science and Technology Journal Database databases were used. The review included studies published in the last 15 years, between February 2009 and February 2024. Quantitative and qualitative empirical studies written in English were included. The following Medical Subject Headings terms in English and Chinese were used for the bibliographic search: regarding the

Figure 1: Diagram.**Fig. 1: Prisma diagram.**

population, “cares,” caregivers” “caregiver,” and “nursing staff”; regarding the problem, “stroke,” “first stroke,” “Cerebrovascular accident,” and regarding processes, “resiliency,” “resilience”.

Initially, 155 articles were identified. After screening according to the inclusion/exclusion criteria, 18 articles were preselected. In case of disagreement, 3 of the 6 researchers attempted to reach consensus on included

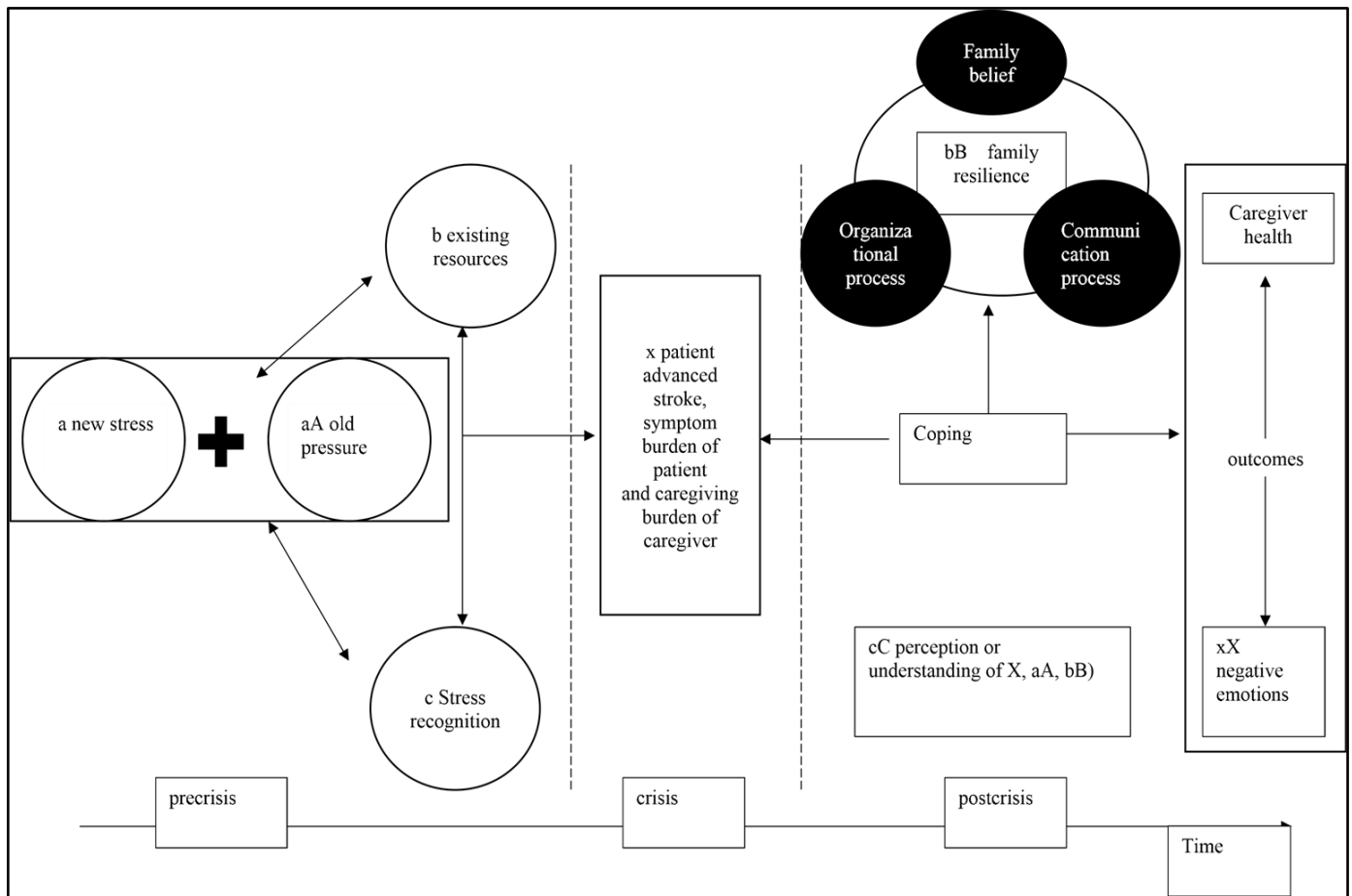


Fig. 2: Family strength and resources.

studies. 1 non-English/Chinese study was excluded. One study was excluded because they did not examine the positive effects of resilience in a clinical context, The full texts of preselected studies were reviewed by a single researcher. Finally, a total of 16 articles were included.⁸⁻²³ (Fig. 1).

Only one summary of the literature¹⁶ is states that the resilience of caregivers. Most used convenient sampling. The samples included the primary caregiver of stroke survivors, most of whom were women. Qualitative studies (n=2) mainly use semi-structured interviews to gather relevant information from caregivers of strokes. By contrast, quantitative studies (n=13) mostly use cross-sectional surveys and vertical studies to describe the data, while summary studies (n=1) are interventions that use a literature summary to evaluate caregiver resilience.

Objective and quality of the studies

A related study²² of the resilience of caregivers in strokes found five dimensions: psychology, social support, personality, psychological elasticity, and cognition. One study⁸ showed a lower level of care burden and a higher quality of life for caregivers with higher psycho-elasticity

scores, response methods and spirituality, while another study¹² identified a regulating role of caregiver resilience in adaptation, significantly lower incidence of primary stroke than recurrence of recurrent stroke, and Wang Jing Yao¹⁸, in the study of family caregivers who survived the primary stroke, had a significant partial indirect impact on their care capabilities through disease uncertainty and recovery.

Resilience of caregiver caring for elderly with stroke

The theoretical framework was built based on the Double ABC-X Model of Family Stress and Coping by McCubbin et al, and Walsh's Family resilience Framework. The Double ABC-X Model of Family Stress and Coping is a theoretical framework used to understand the process families go through when they experience stress. Developed by Reuben Hill, this model highlights the factors that influence a family's response to stressors. The model consists of four major components: the stressor, the family's resources and coping strategies, the family's definition of the stressor, and the family's ability to manage and cope with the stressor.

The original ABC-X model was expanded to the Double ABC-X model by McCubbin and Patterson, which emphasizes the importance of the “pile-up” of stressors and the family's ability to handle them. which emphasizes that the effect of cognitive appraisal and coping on individual outcomes, also a crisis (X) is not solely determined by the stressor (A) itself, but rather by the interplay of three key factors.

The second is Walsh's Family Resilience Framework, which consists of three key processes in family coping, including family belief, organizational process, communication process. Overall, the framework highlights the importance of family strengths and resources in promoting resilience in the face of challenges. The theoretical framework of this study is shown in Fig. 2. Variables affecting resilience

Most of the research finds that the following five dimensions mainly affect the resilience of caregivers. The mental health of the caregiver is one of the important indicators for assessing their resiliency, covering mental health indicators such as anxiety, depression, and stress levels. Their response strategies are also key factors, including positive response (such as problem-solving, seeking social support) and negative response (e.g. escape, denial).²⁴ Some studies have shown that high resilience scores are linked to positive response strategy.²⁵

In addition, social support from family, friends, communities or professional institutions also has an impact on their resilience.²⁶ Assessing the burden of caregivers in providing care services and their available response resources, such as time, money, energy, etc., are factors that must be taken into account. Individual factors of caregivers include genetic, gene, gender, age, health, etc. can also affect caregiver's resilience levels, some of whom are innately more resilient, and others may need more time and resources to adapt and respond to challenges. Self-efficacy reflects the degree of confidence that caregivers are able to deal with difficulties and challenges effectively.²⁷

Determine factors of resilience

Wang²⁰ discovered a favorable relationship between caregiver quality of life and resilience, indicating that resilience enhances mental health and survival while sharply lowering the risk of stress, anxiety, and depression. A study by Fang et al,¹¹ stated that resilience acts as an intermediary between the care burden and the symptoms of depression, suggesting that more resilient caregivers are less susceptible to the adverse effects of care stress. Resilience can reduce caregiver's negative emotions, such as anxiety, depression, emotional distress,

and can help them adapt actively to the challenges of stroke and help them develop effective response strategies.²⁸

Social support from family, friends and healthcare providers appears to be the cornerstone of the resilience of caregivers.^{17,19,22} Epidemiological studies²⁹ showed that resilience plays a major role in increasing interpersonal and perceptual social support. Several studies included in this review emphasize the protective role of resilience in mitigating the negative psychological consequences of care.^{11,20,21}

A systematic review by Qureshi et al,¹⁶ showed that interventions combining information provision, problem-solving skills training and psychoeducation contributed to improving the resilience of caregivers. Taking everything into account, the reviewed research indicate that resilience is a dynamic phenomenon that arises from the interplay of various personal and environmental elements and may lessen the adverse consequences of providing care for elderly stroke victims.

Care burden experienced by caregivers

Caregivers may suffer from physical exhaustion, pains in their muscles, and injuries as a result of the strain of helping with everyday tasks or transfers. Anxiety, sadness, and a sense of loneliness might be psychological effects of the ongoing stress of providing care. Socially, caregivers who find their spare moments taken by taking care of others may find it difficult to maintain connections and may ignore personal hobbies. When they see their loved one deteriorate or deal with the difficulties of being a caregiver, they might experience feelings of shame, rage, and frustration.

Caregiver burden in stroke care

The elderly have a higher chance of complications from stroke and a more difficult recovery process due to the prevalence of other chronic diseases and health issues. As a result, some elderly persons may pass away or have permanent incapacity.³⁰ The recurrent stroke occurs more frequently in older individuals due to risk factors such as diabetes and high blood pressure. Therefore, in order to prevent recurrence, senior citizen individuals with stroke require long-term monitoring and care.

Factors influencing caregiver burden

The discussion begins with caregivers' own conditions, such as psychological resilience, health level, and social support, may affect their ability to withstand the stress of caregiving. More recent evidence^{8,9,11-13,15,17-19,21-23} has confirmed that caregivers with higher levels of resilience are generally better able to cope with the stress of

caregiving. Positive coping mechanisms including accepting reality, actively seeking out assistance, and seeking solutions to issues are common among those caregivers, and they also have a higher chance of maintaining mental health. In addition, the poor health of caregivers can lead to problems such as physical exhaustion and depression, which will increase the physical and mental burden on caregivers.¹¹

Several studies^{13,19} have reported that the degree of social support caregivers feel is closely related to their level of burden. The support of social networks also plays a positive role in reducing the burden on caregivers.¹⁹ Secondly, the condition and degree of functional impairment of stroke patients are also important factors affecting caregiver burden. Several studies^{13,17} report that the lower the patient's ability to perform daily activities, the higher the need for care, which results in more effort and time required for caregivers, thereby increasing their burden.

A number of studies reported^{11,12,21,23} relationship between the length and severity of a patient's care requirements and the caregiver load that follows. Long-term caregivers tend to experience higher levels of depression and anxiety.

Finally, socioeconomic factors also influence caregiver resilience and burden.^{22,23} Educational level, income, and religious affiliation may influence caregiver burden levels. People with religious beliefs have lower levels of caregiver burden than people without religious beliefs. Current research has uncovered the iceberg tip of the factors affecting the care burden of elderly stroke patients. We need more research to develop effective support to help caregivers cope with stress, improve quality of life, and ultimately provide better care for stroke patients.

Limitations

Firstly, most studies employ a quantitative approach, limiting in-depth understanding of the experiences and perspectives of caregivers. The cultural context of caregiving is not always addressed. Last, most studies focused on caregivers in China, and the generalizability of these findings to other populations needs further investigation.

CONCLUSION

Caregiver resilience is a vital factor in promoting positive outcomes for both stroke patients and their caregivers. By incorporating strategies to assess and promote resilience into routine clinical practice, healthcare professionals can empower caregivers to cope more effectively with the challenges they face and improve the overall well-being of the stroke caregiving dyad.

Future directions

Further research is needed to explore the effectiveness of different resilience-building interventions for stroke caregivers. Additionally, longitudinal studies can provide a deeper understanding of the long-term impact of resilience on caregiver well-being and stroke patient outcomes. Finally, including qualitative research can offer richer insights into the experiences of caregivers and the factors that contribute to their resilience.

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REFERENCES

1. Mulimani N. Study of Clinical Profile, Electrocardiographic and Echocardiographic Changes in Patients with Cerebrovascular Accidents: Rajiv Gandhi University of Health Sciences (India); 2019.
2. Khan SU, Khan MZ, Khan MU, Khan MS, Mamas MA, Rashid M, et al. Clinical and economic burden of stroke among young, midlife, and older adults in the United States, 2002-2017. *Mayo Clin Proc* 2021;5:431-41.
3. Xia X, Yue W, Chao B, Li M, Cao L, Wang L, et al. Prevalence and risk factors of stroke in the elderly in Northern China: data from the National Stroke Screening Survey. *J Neurol* 2019;266:1449-58.
4. Hartford W, Lear S, Nimmon L. Stroke survivors' experiences of team support along their recovery continuum. *BMC Health Services Res* 2019;19:1-12.
5. Mallikarjuna Reddy D, Salikar RP. Clinical Study of Risk Factors, Pattern of Clinical Presentation and Correlation with Imaging in Acute Stroke. *Int J Med Pharmaceut Res* 2023;4:530-6.
6. Hartmann S, Backmann J, Newman A, Brykman KM, Pidduck RJ. Psychological resilience of entrepreneurs: A review and agenda for future research. *J Small Business Management* 2022;60:1041-79.
7. Zheng P, Gray MJ, Duan W-J, Ho SM, Xia M, Clapp JD. An exploration of the relationship between culture and resilience capacity in trauma survivors. *J Cross-Cultural Psychol* 2020;51:475-89.
8. Zhou Zhenfeng LM, Jiang Wenbin, Li Xiao, Yongmei J. Construction and application of family resilience intervention program for caregivers of first-episode stroke patients. *J Nursing* 2024;28:5-10.
9. Chow EO, Wong YY, Fok DY, Liao X, Li C. Positive life stories of Stroke-Survivor's spousal caregiving in Hong

- Kong: Lessons for policy and practice. *Soc Sci Med* 2021;291:114476.
10. El Masry Y, Mullan B, Hackett M. Psychosocial experiences and needs of Australian caregivers of people with stroke: prognosis messages, caregiver resilience, and relationships. *Topics Stroke Rehabil* 2013;20:356-68.
11. Fang L, Dong M, Fang W, Zheng J. Relationships between care burden, resilience, and depressive symptoms among the main family caregivers of stroke patients: A cross-sectional study. *Front Psychiatry* 2022;13:960830.
12. Gao X. The influence of caregiver burden and family resilience on family adaptation in stroke patients' family caregivers. Master's thesis, Yanbian University. 2018.
13. Huan S. Study on the burden of primary caregivers of stroke patients based on the family resilience model. Master's thesis, Yang Zhou University 2023.
14. İnci FH, Temel AB. The effect of the support program on the resilience of female family caregivers of stroke patients: Randomized controlled trial. *Appl Nursing Res* 2016;32:233-40.
15. Jia Y, Shi J, Sznajder KK, Yang F, Cui C, Zhang W, et al. Positive effects of resilience and self-efficacy on World Health Organization Quality of Life Instrument score among caregivers of stroke inpatients in China. *Psychogeriatrics* 2021;21:89-99.
16. Qureshi A, Swain N, Aldabe D, Hale L. Exploring challenges affecting resilience in carers of stroke survivors: A qualitative descriptive study. *Disability and Rehabilitation* 2023;45:3696-704.
17. Shi H, Gu Z, Liao Y, Wan X, Ji L. The mediating effect of family resilience on the daily living ability of stroke patients and the burden of primary caregivers. *J Nursing* 2023;17:53-6.
18. Wang J, Cui J. Resilience and caregiving ability among caregivers of people with stroke: The mediating role of uncertainty in illness. *Front Psychiatry* 2022;13:788737.
19. Wang S, Lu Q, Zhang D, Wang L, Jin H, Zhou Y, Ma R. Mediation effect of self-efficacy on the relationship between perceived social support and resilience in caregivers of patients with first-stroke in China: a cross-sectional survey. *Topics Stroke Rehabil* 2024;1-9. doi.org/10.1080/10749357.2024.2318087
20. Wang Z. A study on the correlation among caregiver burden, family resilience, and quality of life of hospitalized stroke patients Master's thesis, Hunan University of Chinese Medicine. 2023.
21. XU C, QI X, WANG X, LI Y. Investigation and analysis the relationship among caring burden, psychological resilience and psychological distress in spouses of dyskinesia stroke survivors. *Chinese J Practical Nursing* 2020;1541-6.
22. Yu M, Li Z, Yan W, Chi Y, Li S, Qiu Z. Status of resilience and its influencing factors among family caregivers of stroke patients. *Chinese Med Innovation* 2022;11:97-100.
23. Zhou Zhenfeng JW, Liu Meiyan, Xue Ting, Li Xiao, Jiang Yongmei. Analysis of current situation and influencing factors of family resilience of young and middle-aged caregivers of stroke patients. *Nursing Rehabil* 2023;22:15-20.
24. Zhang J, Yang Z, Wang X, Li J, Dong L, Wang F, et al. The relationship between resilience, anxiety and depression among patients with mild symptoms of COVID-19 in China: A cross-sectional study. *J Clin Nursing* 2020;29:4020-9.
25. Askeland KG, Bøe T, Breivik K, La Greca AM, Sivertsen B, Hysing M. Life events and adolescent depressive symptoms: Protective factors associated with resilience. *PloS one* 2020;15(6):e0234109.
26. Li Y, Cao G-y, Jing W-z, Liu J, Liu M. Global trends and regional differences in incidence and mortality of cardiovascular disease, 1990– 2019: findings from 2019 global burden of disease study. *Eur J Preventive Cardiol* 2023;30:276-86.
27. Sagone E, De Caroli ME, Falanga R, Indiana ML. Resilience and perceived self-efficacy in life skills from early to late adolescence. *Int J Adolescence Youth* 2020;25:882-90.
28. Hamama-Raz Y, Nissanholtz Gannot R, Michaelis M, Beloosesky Y, Nissanholtz A. Informal caregivers' negative affect: The interplay of caregivers' resilience, aging anxiety and burden. *Aging Mental Health* 2023;27:1300-6.
29. Sippel LM, Pietrzak RH, Charney DS, Mayes LC, Southwick SM. How does social support enhance resilience in the trauma-exposed individual? *Ecol Society* 2015;20:1-9.
30. Kernan WN, Viera AJ, Billinger SA, Bravata DM, Stark SL, Kasner SE, et al. Primary care of adult patients after stroke: a scientific statement from the American Heart Association/American Stroke Association. *Stroke* 2021;52:e558-e71.

Long-term follow up of a patient with Camurati–Engelmann disease: Case report and literature review

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Camurati-Engelmann disease is an exceedingly rare genetic disorder characterized by distinct radiological features that differentiate it from other osteo-dysplastic diseases. A 52-year-old woman presented with a 20-year history of right hip pain with recent exacerbation over 18 months. Diagnostic evaluation included bone scintigraphy, radiography, and blood tests. Bone scintigraphy revealed symmetrically increased uptake throughout the diaphysis of long bones and skull, while radiography showed cortical thickening and coarse trabeculation with bilateral enlargement of multiple

bones. These findings indicated diffuse diaphyseal sclerosis, consistent with Camurati–Engelmann disease. She was managed with analgesics, anti-inflammatory agents, and intermittent intralesional steroid injections for over 7 years, during which no additional radiographic changes were noted. Therefore, we aim to report this case and conduct a literature review.

Keywords: Camurati–Engelmann disease, progressive diaphyseal dysplasia, bone scintigraphy.

INTRODUCTION

Camurati–Engelmann disease (CED), also known as progressive diaphyseal dysplasia, is a rare autosomal dominant skeletal disorder. The general clinical manifestations vary, with common symptoms including extremity pain (68%), waddling gait disturbance (48%), fatigue (44%), muscle weakness, and reduced muscle mass (39%).¹⁻³ The hallmarks of CED are bilateral and symmetrical hyperostosis, cortical thickening, endosteal bony sclerosis, and narrowing of the medullary cavity in the long bones' diaphysis (94%) on imaging studies, which can progress to metaphysis while sparing the epiphyses.¹⁻⁴

Bone scintigraphy emerges as a pivotal diagnostic tool, detecting increased osteoblastic activity even preceding radiographic evidence of diaphyseal sclerosis,³ facilitating early diagnosis and disease severity assessment superior to radiography alone.⁵ A combined approach integrating radiological and scintigraphic findings is recommended for a definitive diagnosis and treatment monitoring.^{5,6} Herein, we report a case of CED with characteristic imaging findings, review relevant literature, and explore the utility of whole-body bone scintigraphy in the early diagnosis and ongoing monitoring of disease activity.

CASE PRESENTATION

A 52-year-old woman presented to our clinic with pain in the right knee for 18 months without any history of injury. She has been receiving treatment for suspected hip joint

inflammation for 20 years and has experienced new-onset finger pain for the past 2 years. She had ulcerative colitis that had been managed with gluco-corticosteroids and



Fig. 1: The low-extremity scanogram revealed thickening diaphyseal cortical, sclerotic and narrowing medullary cavity, expanded diaphyseal segment in bone of lower and extremities. After 7 years, there was little change in the extent of sclerosis and diaphyseal expansion; however, there appeared to be further progression of valgus deformity.

mesalazine. Physical examination revealed a valgus deformity, localized swelling, and tenderness in the right knee.

Blood tests showed insufficient 25-OH Vitamin D3 levels at 24.37 ng/mL (insufficiency: 10–30 ng/mL), elevated anti-nuclear antibodies, and normal erythrocyte sedimentation rate, C-reactive protein, calcium, serum phosphorus, serum alkaline phosphatase, parathyroid hormone, thyroid-stimulating hormone levels. The renal function tests were normal. Levels of bone turnover markers were normal, with osteocalcin at 16 ng/mL (within the normal range for individuals aged 20 years to premenopausal: 11–43 ng/mL) and C-telopeptide of collagen at 0.565 ng/mL (within the normal range for premenopausal women, <0.583 ng/mL).

Rheumatoid antibody tests for HLA B27, anti-cyclic citrullinated peptide antibody, anti-SS-A antibody, anti-SS-B antibody, anti-ds DNA IgG, anti-Smith antibody, anti-RNP antibody, and Rheumatoid Factor was unremarkable.

Low-extremity scanogram showed bilateral femur, tibia, and fibula enlargement with cortical thickening and trabeculation (Fig. 1A). Bone scintigraphy revealed symmetrical increased uptake along the long bones of the upper and lower extremities and skull (Fig. 2). Radiologic

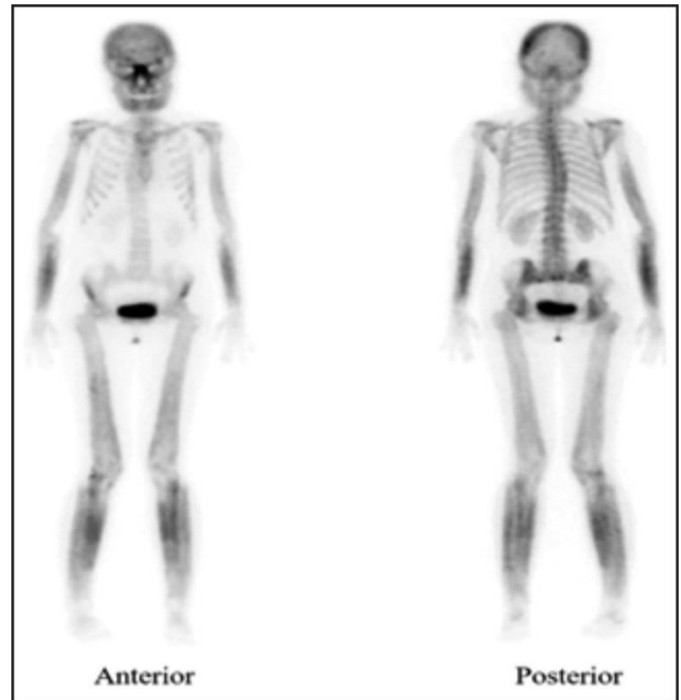


Fig. 2: Whole body bone scan showing diffuse, bilateral, symmetric increased uptake in the diaphysis of the long bones of lower and upper extremities, and the skull. In addition, valgus deformity of the knees exhibited.

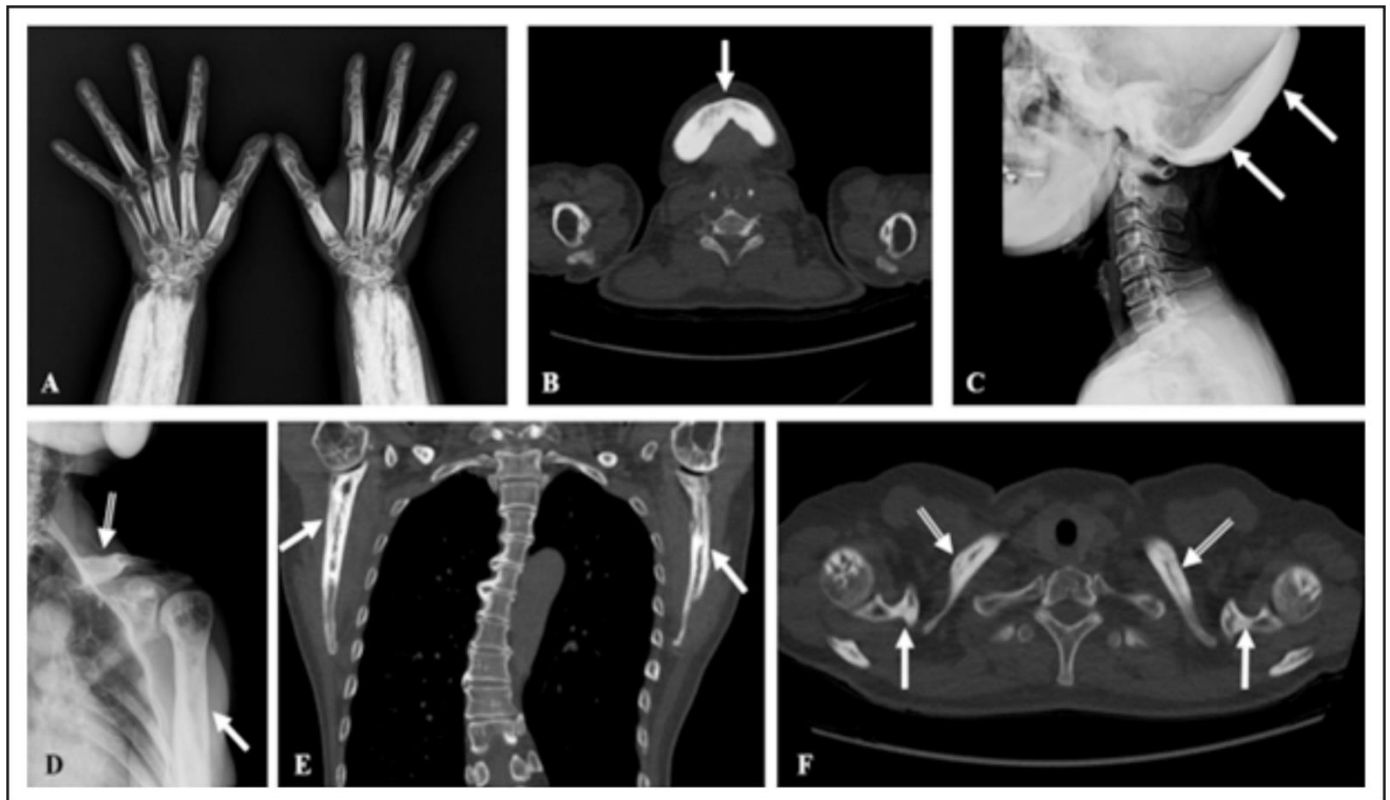


Fig. 3: The imaging findings of (A) the metatarsal and phalangeal bones of both hands, (B) mandible, (C) occipital bone and skull base, (D, F double line arrows) clavicles, and (E, F, white arrows) scapulae are depicted. Cortical thickening, narrowing of the medullary cavity, and trabeculation are observed in all images, showing a similar pattern.

evaluation of the hands, skull, and shoulder showed similar findings (Fig. 3). Bone mineral densitometry showed diffuse elevation in the lumbar 2–3 spine and left proximal femur, with Z scores of 1.671 and 2.496, respectively, consistent with the findings of hyperostosis. CED was diagnosed.

Genetic testing for confirmation was not conducted due to the patient's refusal. Treatment included anti-inflammatory drugs, analgesics, and intermittent glucocorticosteroids. In case of severe symptoms, intralesional steroid injection was administered. After 7 years, no significant changes were observed in radiographs or symptoms (Fig. 1B).

DISCUSSION

CED diagnosis poses challenges due to its rarity, progressive nature, and genetic origin, leading to varied clinical and radiological presentations. Early diagnosis is important because the onset of the disease is usually during childhood.³ Diagnosis relies on a multifaceted approach, encompassing molecular genetic studies for transforming growth factor beta 1 (TGFβ1) mutations, family history, clinical manifestations, and combined imaging studies, including radiography and bone scintigraphy.

Radiographically, CED shows diaphyseal sclerosis in long bones, such as femur (98%), tibia (96%) humerus (88%), radius (87%), ulna (85%), and progressing to metaphysis while sparing epiphyses.^{3,4} Advanced stages may involve extensive skeletal regions, including skull (54%), pelvis (63%), mandible, vertebra, and metatarsal and metacarpal bones.^{3,4,7} Patients with CED manifest musculoskeletal abnormalities such as scoliosis, kyphosis, lordosis, coxa valga, genu valgum, and pes planus.⁶ Uncommon symptoms include facial paralysis, hearing difficulty (18%), visual manifestations due to compressive optic neuropathy as the latest complaint, and decreased subcutaneous fat (21%).^{3,5,6}

CED is a rare genetic progressive bone disease. The diagnosis relies on genetic testing for TGFβ1 mutations,^{4,5} primarily occurring in chromosome 19q13, affecting the latency-associated peptide encoding region in 94% of cases.^{3,8} Mutations in TGFβ1, either type I or II,⁴ underpin CED pathogenesis, disrupting bone metabolism by impeding osteoblast activity and enhancing osteoclast function.⁵ Consequently, TGFβ1 inhibits myogenesis and adipogenesis resulting in decreased muscle mass and subcutaneous fat.³

While several bone dysplasias share clinical and radiological features with CED, distinctions exist. Conditions like craniofacial dysplasia and Kenny–Caffey syndrome type 2 present with similar craniofacial abnormalities but differ in characteristics such as

dwarfism. Conversely, juvenile Paget's disease is typified by bowing of long bones and coarse trabeculations, distinguishing it from CED. Diaphyseal dysplasia with anemia, characterized by the absence of subperiosteal bone formation and frequent infections, contrasts with CED.

Hyperostosis corticalis generalisata–Worth type can be distinguished by the presence of endosteal thickening without widening of the diaphyseal shaft or mandible.⁹ Van Buchem disease primarily manifests secondary symptoms (e.g., macrocephaly, visual and hearing problems) due to hyperostosis of the skull and mandible.¹⁰ The most challenging condition to differentiate is Ribbing disease, which presents with involvement of the diaphysis of long tubular bones while sparing the epiphyses. Ribbing disease exhibits asymmetry even when it is unilateral or bilateral.⁹

Glucocorticoid inhibits bone formation by impeding osteoblast proliferation and bone matrix synthesis, while also promoting osteoclast proliferation.^{3,6} The treatment effect of Bisphosphonates and calcitonin efficacy in CED treatment remains contentious,³ while angiotensin II type 1 receptor antagonist decreases pain and increases muscle strength through TGFβ receptor inhibition, warranting further exploration as maintenance therapy.⁶

In summary, diagnosing CED poses challenges due to its rarity, requiring a high index of suspicion and comprehensive assessment of radiological and clinical features. Bone scintigraphy emerges as a valuable diagnostic tool, detecting characteristic diffuse, bilateral, and symmetric intense uptake in the long bones of the extremities while sparing epiphyses. Early diagnosis is crucial, not only for enhancing clinical outcomes but also for preserving quality of life by addressing progressive sclerotic changes.

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REFERENCES

1. Brat HG, Hamoir X, Matthijs P, Lambin P, Van Campenhoudt M. Camurati-Engelmann disease: a late and sporadic case with metaphyseal involvement. *Eur Radiol* 1999;9:159-62.

2. Grey AC, Wallace R, Crone M. Engelmann's disease: a 45-year follow-up. *J Bone Joint Surg Br* 1996;78:488-91.
3. Janssens K, Vanhoenacker F, Bonduelle M, Verbruggen L, Van Maldergem L, Ralston S, et al. Camurati-Engelmann disease: review of the clinical, radiological, and molecular data of 24 families and implications for diagnosis and treatment. *J Med Genet* 2006;43:1-11.
4. Yuldashev AJ, Shin CH, Kim YS, Jang WY, Park MS, Chae JH, et al. Orthopedic Manifestations of Type I Camurati-Engelmann Disease. *Clin Orthop Surg* 2017;9:109-15.
5. Xie P, Huang JM, Li HL, Huang XJ, Wei LG. Camurati-Engelmann disease-a rare cause of tetany identified on bone scintigraphy: A case report. *Medicine (Baltimore)* 2017;96:e7141.
6. Kim YM, Kang E, Choi JH, Kim GH, Yoo HW, Lee BH. Clinical characteristics and treatment outcomes in Camurati-Engelmann disease: A case series. *Medicine (Baltimore)* 2018;97:e0309.
7. Zhang LL, Jiang WM, Yang HL, Luo ZP. Treatment of Ribbing disease with 5-year follow-up and literature review. *Osteoporos Int* 2017;28:1499-502.
8. Qin Y, Tang S, Zhen G, Ding Q, Ding S, Cao X. Bone-targeted delivery of TGF-beta type 1 receptor inhibitor rescues uncoupled bone remodeling in Camurati-Engelmann disease. *Ann N Y Acad Sci* 2018;1433:29-40.
9. Baretic M, Korsic M, Potocki K, Horvatic GH, Orlic ZC. Camurati-Engelmann disease in a family from Croatian Island: an old bone scan confirmed pattern of inheritance. *Coll Antropol* 2014;38:755-8.
10. Maheshwari S, Yangzom S, Bhanu KU, Rajesh U, Narayan A. Van Buchem Disease: First Case Report from the Indian Subcontinent with an Early Presentation. *J Child Sci* 2021;11:e38-e41.

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