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Metabolic Syndrome and Serum Liver Enzymes Level at Patients with Type 2 Diabetes Mellitus

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ABSTRACT

Objectives: The aim of this study was to evaluate liver function in patients with type 2 diabetes mellitus (T2DM) with and without metabolic syndrome (MS) by determining serum levels of gamma glutamyltransferase (GGT), alanine aminotransferase (ALT) and aspartate aminotransferase (AST). We also investigated correlation between levels of liver enzymes and some components of MS in both groups of patients. **Methods:** This cross-sectional study included 96 patients (age 47–83 years) with T2DM. All patients were divided according to the criteria of the National Cholesterol Education Program (NCEP) in two groups: 50 patients with T2 DM and MS (T2DM-MS) and 46 patients with T2DM without MS (T2DM-Non MS). The analysis included blood pressure monitoring and laboratory tests: fasting blood glucose (FBG), total lipoprotein cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), triglyceride (TG), fibrinogen and liver enzymes: GGT, ALT and AST. T2DM-MS group included patients which had FBG ≥ 6,1 mmol/L, TG ≥ 1,7 mmol/L and blood pressure ≥ 130/85 mm Hg. **Results:** T2DM-MS patients had significant higher values of systolic blood pressure, diastolic blood pressure and medium arterial pressure compared to T2DM-Non MS patients. Serum levels of TC, TG, LDL-C, VLDL-C and FBG were significantly higher in the T2DM-MS group compared to the T2DM-Non MS group. Serum fibrinogen level and GGT level were significantly higher in patients with T2DM-MS compared to the serum fibrinogen level and GGT level in T2DM-Non MS patients. Mean serum AST and ALT level were higher, but not significantly, in patients with T2DM and MS compared to the patients with T2DM without MS. Significant negative correlations were observed between TC and AST ($r= -0,28$, $p<0,05$), as well as between TC and ALT level ($r= -0,29$, $p<0,05$) in T2DM-MS group of patients. **Conclusion:** These results suggest that patients with T2DM and MS have markedly elevated liver enzymes. T2DM and MS probably play a role in increasing the risk of liver injury.

Key words: Diabetes mellitus, metabolic syndrome, liver enzymes.

1. INTRODUCTION

Several prospective population studies have suggested that increased concentrations of hepatic enzymes in serum, even within the reference interval, may be associated with increase in the risk of type 2 diabetes mellitus and the metabolic syndrome, as well as death (1, 2, 3).

The metabolic syndrome is a group of risk factors which increase the risk of cardiovascular diseases and type 2 diabetes more than the individual components (abdominal obesity, increased serum triglycerides, low high-density lipoprotein (HDL) cholesterol, hyperglycemia and hypertension) (4).

The metabolic syndrome, in part through glucose intolerance and insulin resistance, is strongly associated with steatosis, fibrosis, and cirrhosis of the liver in severely obese adults (5).

Circulating concentrations of the liver transaminases: alanine aminotransferase (ALT), aspartate aminotransferase (AST) and to less extent gemma-glutamyltransferase (GGT) are commonly used as markers of liver damage due to fatty acid infiltration and inflammatory stimuli. Recent findings indicate that serum levels of these enzymes are associated with multiple components of the metabolic syndrome (6).

Alanine aminotransferase (ALT) is the most specific marker of this liver pathology. Recent data shows there is significant association between increased ALT and insulin resistance, type 2 diabetes, and the metabolic syndrome (7).

Increases in ALT are positively associated with each component of the metabolic syndrome, increased TG, glucose, waist circumference, diastolic blood pressure, and reduced HDL-C levels (8).

In a prospective study in Pima Indians, serum ALT concentrations were related to both hepatic insulin resistance and later decline in hepatic insulin sensitivity. In contrast, aspartate aminotransferase (AST) and gamma glutamyltransferase concentrations were unrelated to changes in hepatic insulin action (9).

Gamma glutamyltransferase (GGT) is considered to be a sensitive but not specific indicator of liver damage. GGT is linked to hypertension in individuals with central adiposity, suggesting the potential for a pathogenic link among fatty liver disease, endothelial dysfunction and cardiovascular risk (10).

More recently, a prospective cohort study of nondiabetic men found that serum GGT, but not AST or ALP levels, were an independent predictor of incident type 2 diabetes (11).

Testing for aspartate aminotransferase, alanine aminotransferase or gemma-glutamyltransferase is part of many routine-screening approaches. Information is lacking on the association of liver enzymes with type 2 diabetes mellitus both with and without metabolic syndrome**.** The aim of this study was to investigate serum GGT, ALT and AST levels in patients with type 2 diabetes mellitus both with and without metabolic syndrome.

2. MATERIAL AND METHODS

This cross-sectional study included 96 patients aged 47-83 years, diagnosed with type 2 diabetes mellitus (T2DM) who were hospitalized at the Clinic for endocrinology, diabetes mellitus and metabolic diseases, Clinical Center University of Sarajevo. Oral medications or insulin therapy are used in the treatment of T2DM.

The metabolic syndrome was defined according to the criteria of the National Cholesterol Education Program (NCEP), based on the presence of 3 or more of the following: waist circumference > 102 cm in men and > 88 cm in women; serum triglycerides ≥ 1,7 mmol/L; HDL cholesterol < 1,04 mmol/L in men and < 1,29 mmol/L in women; blood pressure ≥ 130 mmHg/ ≥ 85 mmHg systolic over diastolic pressure; fasting blood glucose ≥6,1 mmol/L (12).

According to the NCEP, patients were enrolled in two groups:

- Group 1: patients with type 2 diabetes mellitus and metabolic syndrome (n=50);
- Group 2: patients with type 2 diabetes mellitus without metabolic syndrome (n=46) as control group.

Group of patients with metabolic syndrome included patients which had fasting glucose level ≥ 6,1 mmol/L,triglycerides ≥ 1,7 mmol/L and blood pressure ≥ 130/85 mm Hg.

Blood samples for analysis were obtained from patients and subjects in fasting conditions from antecubital vein into siliconized tubes (BD Vacutainer Systems, PL6 7BP, Plymouth, UK.). Plasma total lipoprotein cholesterol (TC) and high-density lipoprotein cholesterol (HDL-C) and triglyceride (TG) levels were determined at the initial assessment using standard enzymatic colorimetric techniques, on automated apparatus (Dimension RxL Max, Dade Behring, Germany) at the Institute for Clinical Chemistry and Biochemistry, Clinical Centre University of Sarajevo.

Low-density lipoprotein cholesterol (LDL-C) levels were calculated using the Friedewald et al. formula (22). Very low-density lipoprotein cholesterol (VLDL-C) levels were calculated by the formula: VLDL-C = TG/2,2 (13).

Fasting blood glucose (FBG) measured using a hexokinase enzymatic method. Normal range for fasting blood glucose in our hospital is between 4,4 and 6,4 mmol/L. Serum gamma glutamyltransferase, alanine aminotransferase, aspartate aminotransferase were measured by the Dimension RXL analyzer (Dade Behring). Plasma fibrinogen was measured by the turbidometric method of Clauss (Dade Thrombin Reagent) (14).

Blood pressure was measured manually in a standardized manner using sphyngomanometer, with the patients in sitting position after five minutes of rest. Values were based on single measurement. Hypertension was defined as a systolic blood pressure of >140 mmHg or a diastolic blood pressure of >90 mmHg or both, with or without the use of blood pressure lowering medications. Medium arterial pressure (MAP) was calculated by the formula: DBP+1/3 (SBP-DBP).

Statistical analysis

Statistical analyses were performed with Statistical Package for the Social Sciences (SPSS) version 13.0 for Windows (Chicago, IL, USA).

Data are presented as mean () ± standard error of the mean (SEM). Data distribution was determined using the Kolmogorov-Smirnov test. Since data were normally distributed, a statistical difference was tested with Student t-tests. Additionally, Pearson correlations were used as measures of association for the continuous variables. Statistical significance was set at p<0,05.

3. RESULTS

All patients (n=96) in our study were confirmed the diagnosis of diabetes mellitus type 2. As defined by the modified National Cholesterol Education Program (NCEP) criteria, 46 or 47,91% patients had metabolic syndrome. The remaining 50 or 52, 09% of patients did not meet the criteria for the diagnosis of metabolic syndrome.

Means of age were similar in both groups of patients and there were no statistically significant differences in age between the two groups.

Table 1 summarizes metabolic syndrome components of the two groups enrolled in the study.

Patients with type 2 diabetes mellitus and metabolic syndrome had statistically significant higher values of systolic blood pressure (SBP), diastolic blood pressure (DBP) and medium arterial pressure (MAP) compared to patients with type 2 diabetes mellitus without metabolic syndrome (p<0,0001).

Mean fasting blood glucose level was significantly higher in the group of patients with metabolic syndrome compared to the patients without metabolic syndrome (17,39 ± 1,05 vs. 13,65 ± 0,71; p<0,01).

Means of HbA1 concentration was lower, but not statistically significant, in the group of patients with type 2 diabetes mellitus and metabolic syndrome compared with the patients with type 2 diabetes mellitus without metabolic syndrome. Subjects with type 2 diabetes mellitus and metabolic syndrome had statistically significantly higher serum concentrations of TC (p<0,001), TG (p<0,0001), LDL-C (p<0,01) and VLDL-C (p<0,001) compared to patients with type 2 diabetes mellitus without metabolic syndrome.

Concentration of HDL cholesterol was lower in the group of patients with DM2 and metabolic syndrome compared with the patients with DM2 without metabolic syndrome, but the difference was not statistically significant.

Mean blood fibrinogen concentration was significantly higher in patients with type 2 diabetes mellitus and metabolic syndrome compared with the patients with type 2 diabetes mellitus without metabolic syndrome (p<0,001).

As shown in Figure 1, patients with type 2 diabetes mellitus and metabolic syndrome had statistically significant higher serum GGT level compared to the patients with type 2 diabetes mellitus without metabolic syndrome (p<0,05). Mean serum AST and ALT level were higher, but not statistically significant, in patients with type 2 diabetes mellitus and metabolic syndrome compared with the patients with type 2 diabetes mellitus without metabolic syndrome (p>0,05). Correlation between liver enzymes and components of metabolic syndrome was observed in both groups of patients.

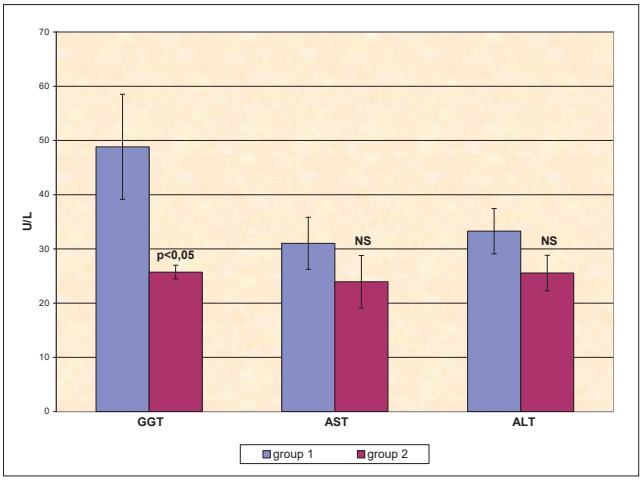

Figure 1. Mean values of serum liver enzymes in both group of patients. group 1–patients with type 2 diabetes mellitus and metabolic syndrome (n=50), group 2–patients with type 2 diabetes mellitus without metabolic syndrome (n=46)

Statistically significant negative association found between serum AST level and total cholesterol serum level (r =–0,28, p<0,05), as well as between serum ALT level and total cholesterol serum level (r =–0,29, p<0,05) in patients with diabetes mellitus type 2 and metabolic syndrome (Table 2).

	Group 1 (n=50)	Group 2 (n=46)	p<
Female gender (%)	60	56,6	NS
Age (years) ($\overline{X}$ ± SEM)	65,6±1,17	64,04±1,62	NS
SBP (mmHg) ($\overline{X}$ ± SEM)	154,1±3,03	130,65±2,80	0,0001
DBP (mmHg) ($\overline{X}$ ± SEM)	93,8±1,70	82,17±1,53	0,0001
MAP (mmHg) ($\overline{X}$ ± SEM)	113,13±1,95	99,04±1,94	0,0001
FBG (mmol/L) ($\overline{X}$ ± SEM)	17,39±1,05	13,65±0,71	0,01
HbA1c (%) ($\overline{X}$ ± SEM)	10,86±0,29	11,11±0,29	NS
TC (mmol/L) ($\overline{X}$ ± SEM)	5,47±0,19	4,5±0,15	0,001
TG (mmol/L) ($\overline{X}$ ± SEM)	3,61±0,42	1,58±0,14	0,0001
LDL cholesterol (mmol/L) ($\overline{X}$ ± SEM)	3,87±0,22	2,95±0,14	0,01
VLDL cholesterol (mmol/L) ($\overline{X}$ ± SEM)	2,29±0,31	0,90±0,15	0,001
HDL cholesterol (mmol/L) ($\overline{X}$ ± SEM)	0,85±0,07	0,95±0,03	NS
Fibrinogen (g/L) ($\overline{X}$ ± SEM)	14,53±0,65	11,17±0,53	0,001

Table 1. Baseline data and components of metabolic syndrome in both groups of patients. Group 1: diabetes mellitus type 2 with metabolic syndrome; Group 2: diabetes mellitus type 2 without metabolic syndrome. SBP-Systolic blood pressure DBP-Diastolic blood pressure; MAP-Medium arterial pressure; FBG-fasting blood glucose; HbA1c-hemoglobin A1c level; TC-total cholesterol; TG-triglyceride; LDL-low density lipoprotein; VLDL-very low density lipoprotein; HDL-high-density lipoprotein; -mean; SEM-standard error of the mean; p-level of statistical significance; NS-not significant.

	Group 1 (n=50)			Group 2 (n=46)		
Variables	GGT (U/L)	AST (U/L)	ALT (U/L)	GGT (U/L)	AST (U/L)	ALT (U/L)
TC (mmol/L)	r = - 0,23	r = - 0,28*	r = - 0,29*	r = 0,22	r = - 0,22	r = 0,07
TG (mmol/L)	r = - 0,01	r = - 0,01	r = 0,05	r = 0,06	r =0,03	r = 0,12
HDL (mmol/L)	r = - 0,10	r = - 0,18	r = - 0,09	r = 0,02	r = - 0,26	r = - 0,06
LDL (mmol/L)	r = - 0,10	r = - 0,23	r = - 0,23	r = 0,26	r = - 0,17	r = 0,15
VLDL (mmol/L)	r = 0,06	r = - 0,06	r = - 0,03	r = 0,16	r = 0,01	r = 0,13

Table 2. Correlation between hepatic enzymes and lipid profile in both group of patients. Group 1: diabetes mellitus type 2 with metabolic syndrome; Group 2: diabetes mellitus type 2 without metabolic syndrome.GGT-Gamma-glutamyl transferase;AST-aspartate aminotransferase;ALT-alanine aminotransferase; TC-total cholesterol; TG-triglyceride; HDL-high-density lipoprotein;LDL-low density lipoprotein; VLDL-vey low density lipoprotein; r=correlation coefficient *= level of statistical significance p<0.05

4. DISCUSSION

The current data concludes that the prevalence of metabolic syndrome in the group of patients with DM type 2 is high and that all of the factors associated with metabolic syndrome had statistically significant higher values in the group of patients with DM type 2 and metabolic syndrome compared to patients with DM type 2 without metabolic syndrome.

In regard to the metabolic syndrome, out of the 96 enrolled diabetic subjects, the prevalence of metabolic syndrome according to NCEP definition was 47,91%. The prevalence of metabolic syndrome in male and female subjects with DM type 2 in Finland and Sweden was 84% and 78% respectively (15), while the prevalence of meta-

bolic syndrome in Ireland was 21% (16). Our figures were lower than those of Finland and Sweden, but higher than the result of Ireland study.

The inconsistency in the prevalence of metabolic syndrome in different studies is largely due to differences in lifestyles, genetic factors or age of the studied populations and on application of different investigation methods (17).

In our study we found that systolic, diastolic and mean arterial pressure were higher among patients with type 2 diabetes mellitus who also has metabolic syndrome.

Sowers and Frohlich confirmed in their study that hypertension occurs approximately twice as frequently in patients with type 2 diabetes mellitus compared with patients without diabetes (18).

The cause of increased blood pressure in most diabetic patients is multi-factorial. Insulin resistance and hyperglycemia may contribute to increase blood pressure, but the mechanisms are still unclear.

Reason may be that inflammation plays a crucial role in the pathophysiology of complications related to metabolic syndrome. In consequence, an increasing degree of vascular inflammation may be important in increasing arterial stiffness and blood pressure in patients with metabolic syndrome. In addition, increased oxidative stress and glycosylation of macroproteins may alter the structure of collagen and elastin, diminishing arterial elasticity (19).

Patients with DM type 2 and metabolic syndrome were more likely to show increased fasting blood glucose concentration and HbA1-hemoglobin level compared to the patients with type 2 diabetes mellitus without the syndrome. This was expected when we know that diabetic patients have a relative insulin deficiency or insulin resistance or even both. Insulin resistance plays an important role in the etiology of the metabolic syndrome (20, 21).

Evident lipid disturbance in subjects with DM type 2 and metabolic syndrome is a low HDL-cholesterolaemia and statistically significantly higher serum concentrations of TC, TG, LDL-C and VLDL-C compared to patients with DM type 2 without metabolic syndrome. These results are consistent with studies elsewhere in the world.

Study of Barrett-Connor et al. confirm that type 2 DM is usually associated with low plasma levels of HDL- C (22).

Numerous earlier studies reported that low HDL-C levels are associated with the metabolic syndrome and diabetes (23, 24, 25). Chahil et al. conducted a study which demonstrated that the prevalence of high plasma TGs levels in individuals with DM was significantly higher than in those without DM (26). Does occurs when insulin deficient or insulin resistance is present lipolysis is accelerated and plasma nonesterified Fatty Acids (NEFA) concentrations rise (27).

Metabolic syndrome is associated with chronic inflammatory response, characterized by abnormal cytokine production, increased acute phase reactants, and activation of inflammatory signaling pathways (28). Low-grade inflammation in people with the metabolic syndrome may be one of the reasons for increased concentration of fibrinogen in plasma.

Our results confirm that patients with DM type 2 and metabolic syndrome were more likely to show increased fibrinogen level compared to the patients with type 2 diabetes mellitus without the syndrome.

There is data that indicates that the fibrinogen increases with age, HbA_{1c}, smoking, hypertension and a number of components of the metabolic syndrome, independent of major confounders (29).

Based on our results it can be concluded that patients with DM type 2 and metabolic syndrome have higher levels of liver enzymes GGT, AST and ALT compared to patients with DM type 2 without metabolic syndrome. We observed a statistically significant negative relationship between serum levels of liver enzymes, AST and ALT and total cholesterol level in group of patients with diabetes mellitus type 2 and metabolic syndrome. We couldn't find such a relationship for GGT although the level of that enzyme was significantly higher in this group than in the group without metabolic syndrome.

Our findings are in agreement with studies of Miyatake et al who found higher hepatic enzymes level, AST,ALT and GGT in subjects with metabolic syndrome compared to control subjects (30).

Kim HC, et al. conducted a study which demonstrated that the serum ALT and GGT levels were significantly associated with metabolic syndrome in men but not in women (31). Nakanishi N et al. suggest that measurement of the serum GGT may be an important predictor for developing metabolic syndrome and type 2 diabetes mellitus in middle-aged Japanese men (32).

According to the study of Wedemeyer et al. elevated ALT level is also a risk factor for non-hepatic diseases including diabetes mellitus type 2, metabolic syndrome, cardiovascular diseases and malignancies (33).

Goessling et al. confirmed that ALT is an independent predictor of metabolic syndrome and diabetes (34) which was in agreement with clinical study done by Kim et al. that confirm increased serum GGT and ALT levels are independent, additive risk factors for the development of type 2 diabetes mellitus in subjects without fatty liver or hepatic dysfunction (35).

Among hepatic enzymes, ALT is the most specific indicator of hepatic pathology in non-alcoholic fatty liver disease and most closely related to liver fat accumulation (36).

GGT is a sensitive marker for liver damage, but less specific than other hepatic enzymes. Rising liver enzymes activity may be manifestation of ongoing low-grade hepatic inflammation or hepatocellular damage, which is common in diabetes and the metabolic syndrome. The raised GGT levels in diabetics with the metabolic syndrome may be result of hepatic steatosis, which could enhance oxidative stress leading to GGT stimulation.

5. CONCLUSION

In conclusion, GGT was significantly higher in patients with type 2 diabetes mellitus and metabolic syndrome than in patients with type 2 diabetes mellitus without metabolic syndrome, while ALT and AST did not show a significant difference.

ALT, AST correlated inversely with TC in patients with type 2 diabetes mellitus and metabolic syndrome. These results suggest that patients with type 2 diabetes mellitus

and metabolic syndrome have markedly elevated markers of liver injury. Follow-up studies are needed to determine whether liver enzymes can be use as hepatic component of the metabolic syndrome.

CONFLICT OF INTEREST: NONE DECLARED.

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