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Role of GGT in diagnosis of metabolic syndrome : A clinic-based cross-sectional survey

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***Background & objectives*: The aim of this study is to know if the liver function tests (LFT), especially gamma glutamyl transferase (GGT), have a predictive value in diagnosis of metabolic syndrome (MS).**

***Methods*: A cross-sectional, single-center study was carried out with 908 subjects. Four hundred and forty two of these subjects were diagnosed with MS with IDF criteria; while other 466 were sex and age matched healthy control subjects. Blood pressure, liver function tests, fasting blood glucose levels and lipid profile of the subjects were recorded.**

***Results*: The mean values of alanine amino transferase (ALT), aspartate aminotransferase (AST) and GGT levels were statistically significantly higher in MS group. The mean values of liver enzymes, for female/ male subjects in MS group, AST; ALT and GGT respectively, were; 20.5/19.7 U/l; 25.9/28.5 U/l; 35.9/42.1 U/l. When the sample is divided into quartiles of the GGT levels, increase in GGT is positively correlated with increased MS prevalence. In ROC analysis GGT is as strongly associated with the IDF diagnostic components as is each individual IDF component, except elevated systolic blood pressure. In covariance analysis, there was significant relationship between elevated GGT levels and MS presence after adjustment for age, sex and MS diagnostic criteria; but not AST and ALT levels. In multivariance analysis, in MS group, a high GGT was positively associated with CVD prevalance (odds ratio: 2.011, 95% CI 1.10-4.57) compared to low GGT group independent of age, sex and smoking habits.**

***Interpretation & conclusion*: Elevated liver enzymes, although in normal ranges, especially at upper quartiles, play a central role in early diagnosis of fat overflow to the liver. Regarding the availability and simplicity of these tests in routine clinical practice, they, especially GGT, have potential to be considered in algorithms for metabolic syndrome.**

Key words GGT - liver function tests - metabolic syndrome

Metabolic syndrome (MS), also known as syndrome X, is associated with high risk for the development of cardiovascular disease (CVD). Since its prevalence is increasing worldwide, a great deal of attention has been directed to this syndrome, in the past several years[1,2]. After the identification of the association of metabolic syndrome with increased cardiovascular disease risk, the diagnosis of metabolic syndrome has

gained more importance. Currently definition of MS, ATP III or International Diabetes Federation (IDF) criteria, include increased waist circumference, raised triglycerides, low HDL, raised fasting glucose and raised blood pressure (BP), are in use[3,4]. Although not well defined, other clinical and biochemical markers associated with MS are known.

Non-alcoholic fatty liver disease (NAFLD), accounting for asymptomatic elevation of aminotransferase levels in up to 90 per cent of cases, is the most frequent cause of abnormal liver function tests results[5].

NAFLD covers a wide spectrum of hepatic lesions including simple fatty infiltration of the liver, steatohepatitis with necroinflammatory changes and a variable degree of fibrosis which may finally progress to liver cirrhosis. Fatty liver is now believed to be an integral part of the metabolic syndrome, since it has been shown to be independently related to insulin resistance independent of obesity and abdominal adiposity[6]. In a study from India, the prevalence of fatty liver is found to be as high as 49 per cent in non-alcoholic patients with type 2 diabetes mellitus[7]. The prevalence of fatty liver disease has been found as high as 20 per cent in some studies accomplished in populations with westernized lifestyles[8,9].

γ-glutamyl transferase (GGT) is shown to be an independent risk factor for the mortality and morbidity of cardiovascular diseases in recent epidemiological and clinical studies[10]. In addition, several prospective studies reported that baseline serum GGT concentration was an independent risk factor for the development of coronary artery disease (CAD), diabetes mellitus, stroke and hypertension[11,12].

Raised liver enzymes, as relatively sensitive and easily obtained markers of NAFLD, reflect chronic ectopic fat deposition in the liver that may be useful in MS diagnosis. With respect to our clinical observations, we hypothesize that high liver function tests, especially GGT levels, are associated with prevalent metabolic syndrome and in this aspect they may have a predictive value in diagnosis of metabolic syndrome. To test this hypothesis we analyzed liver function tests (ALT, AST and GGT), blood pressure, fasting blood glucose levels and lipid profile, body mass index, and waist circumference of subjects without any known hypertension, diabetes mellitus, impaired fasting glucose and hyperlipidemia. By this way, we aimed to show the importance of liver function tests, especially GGT, in diagnosis of metabolic syndrome.

Subjects & Method

Survey design: A cross-sectional, single-center study was carried out between October 2007 and June 2008, in Fatih University Hospital, with 908 subjects who were admitted to our Internal Medicine, Gastroenterology and Endocrinology outpatient clinics without any known hypertension, diabetes mellitus, impaired fasting glucose and hyperlipidemia.Four hundred and forty two of these subjects (191 men, 251 women) were diagnosed with MS with IDF criteria; while other 466 were (180 men, 286 women) sex and age matched healthy control subjects.

Standing body height was measured with a commercial stadiometer. A digital scale, with an accuracy of ±100 g, was used to measure body weight (BW). The waist circumference (WC) was measured in a horizontal plane, midway between the inferior margin of the ribs and the superior border of the iliac crest. Body mass index (BMI) (kg/m^2) was calculated by dividing weight (in kilograms) by the square of height (in meters).

Blood pressure was also recorded after at least 5 min of rest in a chair, with feet on the floor, and arm supported at heart level, using a mercury sphygmomanometer. An appropriate-sized cuff (cuff bladder encircling at least 80% of the arm) was used to ensure accuracy. Systolic blood pressure was measured at the point where the first of two or more sounds was heard (phase 1), and diastolic blood pressure before the disappearance of sounds (phase 5).

Blood samples of 5 ml were drawn after 8-12 h overnight fasting for the measurement of lipid profile [total cholesterol, high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) and triglycerides (TG)], liver function tests [Alanin transaminase (ALT), aspartate transaminase (AST) and Gama-glutamyl trasferase (GGT)], and fasting plasma glucose levels. Plasma glucose was measured using the glucose oxidaseperoxidase method, serum total cholesterol and triglycerides by standard enzymatic procedures and HDL cholesterol by direct assay method[13-16]. T2DM and impaired fasting glucose were diagnosed according to the diagnostic criteria of the American Diabetes Association[17].

ALT, AST and GGT were assessed with a Roche/ Hitachi 902 using the companion's original kits (Roche

Diagnostics, GmBH, Mannheim, Germany). The intra-assay and interassay coefficient of variation was <5 per cent for ALT, AST and GGT. Reference ranges for ALT, AST and GGT were < 40 U/l, 1-31 U/l and 1-32 U/l, respectively.

Cardiovascular disease (CVD) was considered to be present if the patients gave a history of any of the following: myocardial infarction, angina pectoris, coronary artery bypass grafting or percutaneous coronary interventions, stroke, transient ischemic attack, arterial thrombosis, peripheral vascular disease, or intermittent claudication.

Patients with hypothyroidism, malignant disease, severe renal insufficiency, cirrhosis, active liver disease attributable to viral infection (positive serology for virus hepatitis B and C), and alcohol consumption were excluded.

The study was approved by the Fatih University Ethics Committee and informed consent was obtained from patients.

Statistical methods: We assessed the association of the standard diagnostic components for MS with LFTs. ROC analysis is used to determine the optimum value of variables in terms of their sensitivity and specificity for predicting MS. The univariate association between CVD status and the presence or absence of raised LFTs and MS and other factors was examined using the Chi-squared test, Fisher's exact test, Student's t-test and the Chi-squared test of trend. Covariance analysis was performed to see the association of liver function tests and MS (correcting for age, smoking, and gender).

Statistical significance was taken as being $P<0.05$. Analyses were performed using SPSS statistical software, version 13 (SPSS Inc., Chicago, IL, USA).

Results

The major biological and clinical characteristics of the study population (n=908) separated between patients with (n=442; %48,7) or without (n=466; % 51,3,) metabolic syndrome are presented in Table I.

Seventeen per cent of overall patients were diagnosed with hypertension and 21 per cent were with dyslipidemia, 4 per cent with diabetes mellitus and 9 with impaired glucose tolerance. Although plasma total cholesterol and LDL-cholesterol levels did not differ between the 2 groups; HDL-C levels were lower and triglyceride levels were higher in MS patients when compared with control group. The mean body mass index value (BMI) was higher in MS group than controls, but the difference was not statistically significant. The mean values of LFT (ALT, AST, and GGT) were statistically significantly higher in MS group (Table I).

We also compared the liver function tests between subjects with or without each component of MS. In this sub criteria analysis, there was no significant difference of age between subjects with or without dyslipidemia and abdominal obesity. However, there was significant difference of age between subjects with or without hypertension, diabetes mellitus and impaired glucose tolerance. The levels of AST, ALT and GGT in subjects with diabetes mellitus, impaired glucose tolerance and abdominal obesity were significantly higher than those in subjects without these components of MS. The highest mean values of liver enzymes has been found in abdominal obesity group (ALT=30.6 U/l; AST= 24.0 U/l; GGT= 43.8 U/l). Only GGT levels were significantly higher in subjects with dyslipidemia than subjects without.

The mean values of liver enzymes, for female/male subjects in control group, AST; ALT and GGT respectively, were; 16.8/19.4 U/l; 17.3/22.4 U/l;

Table I. Biological and clinical characteristics of the study population

	MS (n:442)	Control (n:466)
Age (yr) (±SD)	51.3 (3.2)	50.2 (3.1)
F/M (%)	274/168 (61.9)	286/180 (61.3)
BMI (kg/m^2) (±SD)	30.8 (4.1)	28.3 (4.3)
HDL (mg/dl) (±SD)	42.1 (9.7)	52.2 (6.9)*
LDL (mg/dl) (±SD)	131.4 (8.9)	115.6 (7.6)
Triglyceride (mg/dl) (±SD)	273.2 (25.8)	114.5 (11.7)*
Waist circumference (cm) (±SD)	104.1 (9.8)	92.4 (6.7)*
Systolic BP (mm Hg) (±SD)	138.2 (11.7)	118.1 (10.5)*
Diastolic BP (mm Hg) (±SD)	86.7 (7.2)	76.5 (5.7)*
AST (U/l) (±SD)	21.1 (9.1)	17.7 (6.3)*
ALT (U/l) (±SD)	26.8 (9.3)	19.2 (4.5)*
GGT (U/l) (±SD)	40.9 (10.2)	21.0 (7.1)*
Current smoker n (%)	25 (5.7)	27 (5.8)
Dyslipidemia (%)	163 (36.8)	27 (5.7)*
DM n (%)	36 (8.1)	0 (0.0)*
IGT n (%)	78 (17.6)	4 (0.8)*
HT n (%)	138 (31.2)	16 (3.4)*
Known CVD n (%)	64 (14.4)	19 (4.0)*

F/M, female/male; BMI, body mass index; BP, blood pressure; DM, diabetes mellitus; IGT, impaired glucose tolerance; HT, hypertension; CVD, cardiovascular disease. *P value < 0.05

18.2/25.7 U/l. There were statistically significant differences between genders in liver enzymes in control group. In MS group, the mean value of these enzymes respectively were; 20.5/19.7 U/l; 25.9/28.5 U/l; 35.9/42.1 U/l and there was statistically significant difference between genders only in GGT levels but not in AST and ALT levels in MS group.

When the sample is divided into quartiles of the GGT levels, increase in GGT is positively correlated with increased metabolic syndrome prevalence. Moreover increased GGT levels were also positively correlated with increased CVD presence.

Table II shows the ROC analysis when GGT is compared with other MS diagnostic criteria. The range of area under curve (AUC) for GGT was: 0.68-0.75. Transaminases displayed a weaker association than GGT for MS: ALT 0.57-0.68, and AST 0.48-0.56. This indicates that GGT is as strongly associated with the IDF diagnostic components as is each individual IDF component, except elevated systolic blood pressure.

The sensitivity and specificity values in diagnosis of MS for some cut off points of GGT for the whole study group is seen in Table III. In ROC curve analysis the optimum cut-off values for GGT were 2O.5 IU for women and 26.5 for men.

In covariance analysis, there were significant relationships between elevated GGT levels and MS presence after adjustment for age, sex and MS diagnostic criteria; but not AST and ALT levels. In multivariance analysis, in MS group, a high GGT was positively associated with CVD prevalance (odds ratio: 2.011, 95% CI 1.10-4.57) compared to low GGT group, independent of age, sex and smoking habits. Similarly, high GGT was positively associated with prevalant CVD in control group (odds ratio: 1.76, 95% CI 1.02-3.91).

Table II. Receiver operating characteristic (ROC) analysis of metabolic syndrome components and liver function tests (LFTs)

Test result variable(s)	Area	95 % confidence interval	
		Lower bound	Upper bound
GGT	.723	.684	.758
Systolic BP	.758	.718	.801
Diastolic BP	.574	.521	.631
AST	.528	.483	.561
ALT	.632	.578	.684
HDL	.674	.641	.712
TG	.672	.633	.712
WC	.712	.682	.738
DM	.834	.796	.868
IGT	.712	.684	.734

BP, blood pressure; DM, diabetes mellitus; IGT, impaired glucose tolerance; HDL, high density lipoprotein; TG, triglyceride; WC, waist circumference

Table III. Sensitivity and specificity of diagnosing MS for some GGT values

GGT (IU/ml)	Sensitivity	Specificity
15.5	0.82	0.36
20.5	0.77	0.62
21.5	0.69	0.65
25.5	0.50	0.81

Discussion

We compared the hepatic enzyme levels in subjects with metabolic syndrome with those age and sex match controls in Turkish population. The predictive ability of increased GGT levels to diagnose MS was higher than hypertriglyceridemia, increased waist circumference and impaired glucose tolerance for both genders. Among the various components of MS, increased systolic blood pressure showed highest predictive ability to diagnose MS in men and increased waist circumference in women.

The ranges of 'normal' values of hepatic enzymes were determined in blood donors long ago. In our study, transaminases are in normal ranges in 91.2 per cent and GGT are in normal ranges in 83.4 per cent of MS patients. Especially ALT and GGT values are significantly higher than control group but still remain in normal ranges. As our results show, normal liver enzymes values could coexist with metabolic syndrome. In a study of Balogun *et al* on 90 patients with type 2 diabetes and 90 nondiabetic controls the ALT and GGT values were significantly higher (52.9 IU/l and 24.3 U/l respectively) in the diabetic group compared to the controls (34.4 IU/l and 9.2 IU/l respectively). Moreover, the most predominant LFT abnormality in diabetic group was found to be isolated elevation of GGT[18].

We showed that liver function tests are higher in subjects with MS than the controls. In some other studies, it has been demonstrated that circulating GGT and transaminases activities are elevated in patients with metabolic syndrome[19,20]. Non-alcoholic fatty liver disease (NAFLD) is a spectrum of liver diseases commonly seen with MS and elevated liver enzymes is a manifestation of fatty liver. NAFLD represents the ectopic fat accumulation in the liver and is now

considered to be the most common cause of chronic liver disease worldwide[21].

Nannipieri *et al* revealed an association with mild elevations in liver function tests and metabolic syndrome[22]. Moreover, Wannamethee *et al*[23] revealed that; elevated levels of ALT and GGT within the normal ranges are found to be the independent predictors of type 2 diabetes mellitus.

GGT is central in glutathione hemostasis that is an important antioxidant defense for the cell. Therefore, GGT plays an important role in antioxidant defense systems[11,12]. Elevated GGT levels could be a marker of oxidative stress and sub clinical inflammation.

In covariance analysis we found a significant relationship between elevated GGT levels and MS presence after adjustment for age, sex and body mass index. Similarly, Rantala *et al* investigated the relationship between GGT and MS and revealed a highly significant relationship between GGT and the components of the metabolic syndrome even after adjustment for age, body mass index and alcohol consumption[24]. In another study of Sakugawa *et al*[25], the serum GGT level found to be correlated with components of MS. Although this relationship between GGT and metabolic syndrome is not clearly understood, some mechanisms including presence of oxidative stress and/or NAFLD can explain the relationship.

Using ROC analysis, we found significant variability in the prediction of MS by IDF diagnostic components, with diabetes mellitus being the strongest and diastolic BP the weakest. The GGT cut-off points were determined from their association with other MS criteria. Interestingly the cut-off point for 'high' GGT is still within the normal laboratory range. In this aspect, we speculate that, clinicians should be aware of the risk of oxidative stress although liver enzymes are in normal ranges especially at upper quartiles.

When we consider GGT above these cut-offs, there was an association with previous CVD in addition to the effect of MS (odds ratio: 2.011, 95% CI 1.10-4.57). This suggests that GGT measures a degree of CVD risk not assessed by standard MS criteria. Recently, Ruttmann *et al*[26] showed that GGT activity was independently associated with cardiovascular mortality; in a large unselected cohort. Some epidemiological studies[27] also suggest that higher serum GGT levels is associated with development of CVD risk factors, including diabetes, hypertension, and the metabolic syndrome.

In conclusion, elevated liver enzymes, although in normal ranges, especially at upper quartiles, play a central role in early diagnosis of fat overflow to the liver. Moreover, GGT may play a role in early diagnosis of metabolic syndrome with a high predictive value for both metabolic syndrome and cardiovascular disease presence. Regarding the availability and simplicity of these tests in routine clinical practice and their universal standardization, these findings indicate the potential of liver enzymes, especially GGT, to be considered in algorithms for metabolic syndrome.

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