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Clinical Investigation

Serum Gamma-Glutamyltransferase Level in Patients with Cardiac Syndrome X

Kardiyak X Sendromu Olan Hastalarda Serum Gama Glutamiltransferaz Düzeyi

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SUMMARY

Objective: *Cardiac syndrome X is still an unknown disease exactly. The most accepted pathogenesis is microcirculatory dysfunction. As an antioxidant, gamma-glutamyltransferase plays an important role in vascular function. In this study we aimed to examine the relation between cardiac syndrome X and serum gamma-glutamyltransferase level.*

Materials and Methods: *The study population consisted of 58 patients and 44 control subjects. Patients fulfilling cardiac syndrome X criteria which are; angina, positive treadmill test and normal coronary angiography, were includedin the study.*

Results: *Both groups were similar in terms of age, body mass index, smoking status and diabetes mellitus history (p=0.686, p=0.424, p=0.76 and p=0.503 respectively). The cardiac syndrome X group consisted of significantly greater number of female and hypertensive patients (p=0.022 and p=0.048, respectively). Baseline laboratory parameters, glucose, creatinine, hemoglobin, lipid profile and liver enzymes were similar for both groups. Cardiac syndrome X group had very significantly higher level of serum gamma-glutamyltransferase level than the control group (p=0.000000006).*

Conclusion: *The present study demonstrated that highly significant relation is found between cardiac syndrome X and serum gamma-glutamyltransferase level.*

Keywords: *Gamma-glutamyltransferase, cardiac syndrome X, microcirculatory function, antioxidant*

ÖZ

Amaç: *Kardiyak sendrom X hâlâ tam olarak bilinmemektedir. En sık kabul edilen patogenez mikrovasküler disfonksiyondur. Bir antioksidan olarak gama-glutamiltransferaz vascular fonksiyonda önemli bir rol oynamaktadır. Bu çalışmada kardiyak sendrom X ile serum gama-glutamiltransferaz düzeyi arasındaki ilişkiyi incelemeyi amaçladık.*

Gereç ve Yöntem: *Çalışma popülasyonu 58 hasta ve 44 kontrol deneğinden ibaretti. Anjina pektoris, pozitif koşu bandı testi ve normal anjiyografi bulguları gibi kardiyak sendrom X kriterlerini karşılayan hastalar çalışmaya alındı.*

Bulgular: *Her iki grup yaş, vücut kitle indeksi, sigara içme durumu ve diabetes mellitus öyküsü açısından benzerdi (sırasıyla, p=0.686, p=0.424, p=0.76 and p=0.503). Kardiyak sendrom X grup anlamlı derecede daha fazla sayıda kadın hasta ve hipertansif hastalardan ibaretti (sırasıyla p=0.022 ve p=0.048). Başlangıçta laboratuvar parametreleri, kreatinin, hemoglobin, lipit profili ve karaciğer enzimleri her iki grupta benzerdi. Kardiyak sendrom X grubunda serum gama-glutamiltransferaz düzeyi kontrol grubuna göre anlamlı derecede daha yüksekti (p=0.000000006).*

Sonuç: *Bu çalışma kardiyak sendrom X ile serum gama-glutamiltransferaz düzeyi arasında yüksek derecede önemli bir ilişkinin bulunduğunu göstermektedir.*

Anahtar kelimeler: *Gama-glutamiltransferaz, kardiyak sendrom X, mikrodolaşım disfonksiyonu, antioksidan*

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INTRODUCTION

Cardiac syndrome X (CSX) is a quite complex entity that is primarily a diagnosis of exclusion [1]. It is defined as normal epicardial coronary artery at angiography with typical angina or angina like discomfort and ischemia documented with stress tests [1]. Even though the epicardial coronary arteries are patent, CSX is not a benign condition. Recent studies demonstrated that CSX patients have poor long- term cardiac outcomes [2-5]. Also the diagnosis is challenging and patient's quality of life and functioning is significantly deteriorated [2]. Although CSX pathogenesis is debatable and various theories have been proposed, the most accepted theory is the abnormal microcirculatory function [6]. The impaired coronary microvascular function has shown to be associated with oxidative stress and increased pro-inflammatory cytokines [7,8]. It is known that elevated oxidative stress causes impaired endothelial function [9].

Gamma-glutamyltransferase (GGT) is a glycoprotein and found in several organs including liver, kidney, vascular endothelium, lung and pancreas [10]. As being a marker of oxidative stress, GGT takes a role in various defense mechanisms in the body as a major antioxidant [10,11]. Several different studies have shown the association between serum GGT activity and cardiovascular and all-cause mortality, stroke, diabetes mellitus and metabolic syndrome. Serum GGT is present in coronary atherosclerotic plaque and plays an important role in the development of atherosclerosis and production of reactive oxygen species [12,13].

In the light of the previous robust data related to antioxidant role of serum GGT, the present study was designed to address the relation between CSX and serum GGT.

MATERIALS and METHODS

Patient population

The study population consisted of 58 patients and 44 control subjects. The study was conducted between April 2013, and October 2014. Patients were included in the study if they fulfilled the CSX criteria: (i); presence of angina or angina equivalent (rest or provacable), (ii); positive treadmill stress test and (iii); angiographically detected normal coronary arteries. Control group was chosen from patients presenting with chest pain to outpatient clinic who had normal treadmill test results. Because the ischemia was ruled out, coronary angiography was not undertaken for the control group. The patients were excluded if they had documented CAD, vasospastic angina, arrhythmias, valvular heart disease, heart failure, vasculitis, myocarditis, connective tissue diseases, acute or chronic hepatobiliary or gastrointestinal diseases, malignancy and those using alcohol and any hepatotoxic drugs including statins and fibric acid derivatives. Also patients with elevated hepatic enzymes were excluded.

The study protocol was approved by the hospital's Ethics Committee and a written informed consent was taken from all study participants.

Data sources

Demographic data and the clinical history of smoking, hypertension, body mass index and diabetes mellitus (DM) were taken at the time of admission to outpatient clinic and recorded digitally. Body mass index was calculated by using [kg/height $(m)^2$] formula.

Venous blood was used for laboratory analysis which was obtained following a fasting period of at least 12 hours. Biochemical parameters were measured using Roche/Hitachi 717 chemi-

cal analyzer (Block scientific, Newyork, USA) modular system.

Treadmill stress testing

The treadmill tests were performed according to Bruce protocol. Twelve leads were monitored during exercise, and recovery period continuously. The test was stopped when symptoms developed (angina, dyspnea) or heart rate of the participant rised to his/her age-adjusted range. Symptoms developed during the exercise were recorded in the treadmill test report. The test was defined positive if typical symptoms developed or ST segment depression (≥ 1 mm downsloping or horizontal after 60-80 ms J point) was detected in at least two leads. Following the treadmill test Duke treadmill score was calculated [14]. Participants with no symptoms and considered to be at low risk according to the Duke treadmill score (Duke treadmill score ≥ 5) were not subjected to coronary angiography.

Coronary angiography

Femoral artery was used for coronary angiography applied by Judkins technique (Siemens axiom 2003). Coronary angiography was performed by an experienced and assistant cardiologist and evaluated by two experienced cardiologist blinded to the study. Angiographic data were recorded digitally. Coronary arteries with any degree of stenosis, luminal irregularity and coronary slow phenomenon were excluded from the study. In order to exclude coronary vasospasm, hyperventilation test was applied. The patients were hyperventilated by breathing deeply and quickly approximately for five minutes.

Statistical analysis

Parametric variables were presented as mean ± SD or median (with interquartile range) and categorical variables as percentages. Kolmogorov-Smirnov test was used for analysing continuous variable for a normal distribution. Differences between continuous variables were evaluated by independent-sample t-test or Mann-Whitney U test. The correlation between categorical variables was assessed by chi- square tests. A two-sided $p<0.05$ was accepted as the level of statistical significance. The statistical analysis was performed by SPSS, version 15.0 for Windows (SPSS, Inc., Chicago, Illinois, USA).

RESULTS

Demographic variables of the study population are shown in Table 1. Both groups were similar in terms of age, body mass index, smoking status and DM history (p=0.686, p=0.424, p=0.76 and p=0.503 respectively). The CSX group consisted of significantly greater number of female participants (p=0.022). Hypertension was more frequent in the CSX group (p=0.048).

Table 1. Demographic and Baseline Clinical Characteristics of the study groups.

	Patient Group	Control Group	p
Age, y	55.3±3.2	55.3±3.8	0.686
Female sex, no (%)	37 (64)	18 (41)	0.022
Body mass index	25.5±1.4	25.7±1.5	0.424
Smoking, no (%)	22 (38)	18 (41)	0.760
Hypertension, no (%)	24 (41)	10 (23)	0.048
Diabetes mellitus, no (%)	18 (31)	11 (25)	0.503

Mann-Whitney U test / Independent t-test

Table 2. Laboratory parameters of study groups.

Parameter	Patient Group	Control Group	p
Glucose, mg/dL	157±51	150±50	0.695
Creatinine, mg/dL	0.8±0.3	0.80±0.2	0.342
Hemoglobin, g/dL	14.5±1.0	14.7±0.9	0.453
Total cholesterol, mg/dL	185.5±9.5	183.5±7.0	0.182
HDL cholesterol, mg/dL	40.3±2.9	40.4±3.5	0.620
LDL cholesterol, mg/dL	121±3.8	121.2±3.8	0.881
Triglyceride, mg/dL	186.0±8.8	183.6±8.9	0.196

Mann-Whitney U test / Independent-samples t-test
HDL: High density lipoprotein
LDL: Low density lipoprotein

Table 2 presented the laboratory parameters of both groups. The CSX and the control groups had similar levels of fasting glucose, creatinine, and hemoglobin levels (p= 0.695, p=0.342 and p=0.453 respectively). Similarly there was no difference in terms of total cholesterol, high density lipoprotein, low density lipoprotein, and triglyceride levels between both groups (p=0.182, p=0.62, p=0.881 and 0.196, respectively). Serum levels of liver enzymes; aspartate amino transferase, alanine amino transferase and alkaline phosphatase were found to be comparable for both groups (p=0.189, p=0.699 and p=0.552, respectively). Cardiac syndrome X group had very significantly higher level of serum GGT level than the control group (p<0.001) (Table 3).

Table 3.

Parameter	Patient Group	Control Group	p
GGT, U/L	44.5±9.5	32.2±9.3	**0.000000006**
AST, U/L	29.1±4.6	27.8±4.3	0.189
ALT, U/L	30.3±6.0	30.1±6.7	0.699
ALP, U/L	132±22.0	130.3±22.0	0.552

GGT: Gamma-glutamyl transpeptidase
AST: Aspartate aminotransferase ALT Alanine aminotransferase
ALP: Alkaline phosphatase

DISCUSSION

The major finding of the present study is that, serum GGT level is significantly elevated in CSX patients probably pointing out to microvascular dysfunction and subangiographic atherosclerosis.

Several studies examined serum GGT activity in acute coronary syndromes [15-20]. Also studies conducted related to ST- elevation myocardial infarction and serum GGT activity have shown similar results. Generally studies in patients with STEMI have demonstrated that serum GGT level was associated with major adverse in-hospital cardiac events and no-reflow phenomenon [15-17]. But Baktir et al. have shown that serum GGT level was not associated with syntax score in STEMI patients [18]. Studies searching the relation between non-STEMI and serum GGT level have in general showed that, serum GGT level was significantly associated with SYNTAX, and Gensini scores, and significant stenosis [19,20]. It is well known that serum GGT plays an important role in the development of atherosclerosis and it is present in coronary atherosclerotic plaque [12,21]. It is well known that non-STEMI is associated with more comorbidities thus the level of atherosclerosis is much higher. This could be the probable explanation.

It is mostly accepted that microvascular dysfunction is the major pathogenesis in CSX patients [6-8]. The increased oxidative stress and pro-inflammatory cytokines play important roles in microvascular dysfunction [8,9]. Cox et al. had previously proposed that endothelial dysfunction could be the pathophysiologic causes of angina in patients with normal coronary angiograms [22]. In another invasive study ran out with intravascular ultrasound showed intimal thickening and atheromatous lesions in non-critical stenosis of coronary arteries in CSX patients [23]. A study performed on patients with coronary slow- flow phenomenon showed that serum GGT level is elevated probably as a result of endothelial and microvascular dysfunction [24]. Two different studies showed that diffuse atherosclerosis using IVUS in coronary slow- flow patients [25,26]. The present study has shown a very significant correlation between serum GGT level and CSX. Similarly designed two studies previously had stated similar results. Demir et al in a smaller-scale study showed that patients with CSX had a higher level of serum GGT level [27]. They also stated that the presence of metabolic syndrome further increases the level of serum GGT level. The present study is conducted with a relatively larger population. We

detected that as the study population getting larger the level of significance is increasing dramatically. In an another much smaller -sized study Yagmur et al demonstrated that the serum GGT level is similar in patients with CSX and coronary artery disease [28]. They also showed that as the level of serum GGT level increases the carotid intima media thickness also increases.

Previous studies have demonstrated that serum triglyceride level, a component of metabolic syndrome, is much higher in CSX patients. In the present study even the level of triglyceride is higher in CSX patients without reaching a level of significance. We thought that this could be happened by chance.

The present study has some limitations. Initially other inflammatory markers like C-reactive protein were not studied. Although the studied population was larger than the previous studies, it was still also a small- sized study. Even though the liver function tests were in normal range the hepatobiliary system was not evaluated with ultrasound. At the institution the study conducted, routinely the ergonovine stress test is not indicated in cases with non-critical lesions. That is why a less reliable test –hyperventilation test- was used to rule out vasospasm. To our opinion this was a limitation. In the present study no intravascular visualizing tests –like intravascular ultrasound- was used. That is why the level of sub-angiographic atherosclerosis could not be assessed.

In conclusion in the present study we demonstrated that serum GGT level is very significantly elevated in CSX patients. As GGT plays an important role in the development of atherosclerosis and production of reactive oxygen species, elevated level of serum GGT level could show that microvascular dysfunction sub-angiographic atherosclerosis could play an important in the pathophysiology of CSX.

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