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Elevated serum gamma-glutamyl transferase activity in patients with cardiac syndrome X and its relationship with carotid intima media thickness

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Objectives — We aimed to evaluate serum gamma-glutamyl transferase (GGT) activity and its relationship with carotid intima media thickness (CIMT) in patients with cardiac syndrome X (CSX).

Methods — The study population consisted of 40 patients with CSX, 35 controls and 40 patients with coronary artery disease (CAD). All patients underwent a noninvasive stress test and conventional coronary angiography. Serum GGT and C-reactive protein (CRP) levels were measured and CIMT was assessed in all subjects.

Results — Serum GGT activity was higher in the CSX and the CAD groups than in the control group (32.6 ± 16.0 and 30.4 ± 15.3 U/L, respectively, vs. 17.9 ± 4.2 U/L; $P < 0.001$). There was no statistically significant difference in serum GGT activity between the CSX and the CAD groups. When compared to the control group, serum CRP levels were significantly increased in both the CSX and the CAD groups (4.1 ± 2.0 and 4.7 ± 2.6 mg/L, respectively, vs. 2.2 ± 1.8 mg/L; $P < 0.001$). Patients with CSX and CAD had significantly higher CIMT values than the controls (0.74 ± 0.17 and 0.94 ± 0.12 mm, respectively, vs. 0.62 ± 0.08 mm; $P < 0.001$). A significant correlation was found between GGT activity and CIMT measurements ($r = 0.640$, $P < 0.001$), but serum GGT activity did not correlate with serum CRP levels in patients with CSX ($r = 0.277$, $P > 0.05$).

Conclusions — The present study showed that serum GGT activity in patients with CSX was as high as those in patients with CAD. Increased GGT levels may play a role in the pathogenesis of the microvascular atherosclerotic process of CSX.

Keywords: *Gamma-glutamyl transferase – cardiac syndrome X – carotid intima media thickness.*

Introduction

Cardiac syndrome X (CSX) is an angina-like chest pain with a positive response to exercise stress testing and normal coronary angiographic findings[1,2]. The exact pathophysiological mechanisms responsible for CSX still remain poorly understood. Arteriosclerosis of the small coronary arteries may be the principal cause of CSX[3]. Microvascular dysfunction, which is also observed in cases of CSX, is associated with proinflammatory cytokines or oxidative stress[4,5].

Serum gamma-glutamyl transferase (GGT) activity has been used as a marker for alcohol consumption or hepatobiliary disease[6]. GGT is a plasma membrane enzyme, which provides antioxidant glutathione resynthesis[7]. Several studies have demonstrated that increased serum GGT activity can be used as a marker for increased oxidative stress in humans[8,9]. Furthermore, it has been shown that GGT activity is directly related to the oxidative events and plays an important role in the evolution of atheromatous plaque[8,10-12].

Since it was shown that serum GGT activity was associated with atherosclerosis and oxidative stress, we hypothesized that serum GGT activity might indeed be associated with CSX and we aimed to evaluate its relationship with carotid intima media thickness (CIMT) in patients with CSX.

Subjects and methods

The study population consisted of 40 patients with CSX, 35 controls and 40 patients with coronary artery disease (CAD). The diagnosis of CSX was established

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according to the presence of anginal chest pain, positive treadmill test and angiographically normal coronary arteries. The control subjects all of whom were similar in the frequency of risk factors, sex and age to the CSX group had experienced atypical chest discomfort, negative treadmill tests and normal coronary angiograms. Patients with CAD were diagnosed by coronary angiography and CAD was defined as coronary artery luminal stenosis of more than 50%. The exclusion criteria were; hypertensive heart disease with left ventricular hypertrophy, valvular heart disease, idiopathic hypertrophic or dilated cardiomyopathy, acute or chronic inflammatory diseases, history of myocarditis and vasculitis, spondyloarthritis, Tietze's syndrome, gastrointestinal tract diseases, diseases of the aorta, hormone replacement therapy, arrhythmias, active hepatobiliary disease and alcohol consumption. The study was approved by the local ethics committee and, all patients and subjects gave written informed consent.

Carotid intima media thickness

CIMT measurements were performed in all patients by vascular ultrasound measurement using a high-frequency ultrasound system (HDI-5000; ATL, Borhell, Washington-USA) and a high frequency vascular transducer (multiple frequency: 7-10 MHz). Both common and internal carotid arteries and carotid bulbi were examined morphologically in detail in all patients. CIMT was measured within the posterior wall of the artery. The average of ten measurements was used to calculate CIMT.

Treadmill exercise stress testing

All treadmill exercise tests were conducted according to Bruce protocol (T600 Treadmill, Spacelabs Burdick, Inc., WI 53531 USA). Three ECG leads (V2, V5 and aVF) were continuously monitored during these tests. A standard 12-lead ECG print was obtained. Total exercise times were recorded in all cases. Electrocardiographic recovery was also continuously monitored, until the depressed ST-segment returned to baseline levels. A positive treadmill test was defined by the occurrence of ischaemic ST-segment depression ($\geq$ 1.0 mm horizontal or downsloping depression at 80 ms from the J point) during treadmill exercise, as measured by several leads on the ECG (usually II, III, aVF, V3–6).

Cardiac catheterization

Coronary angiography was performed using the Judkins technique in all patients (Philips Medical Systems Integris H 3500 ve 5000). Coronary arteries were classified as normal on the basis of visual assessment of the absence of any luminal irregularity. To exclude the possibility of coronary artery vasospasm, all patients underwent a hyperventilation test during coronary angiography, which was performed by asking the patients to breathe quickly and deeply for 5 minutes. CAD was defined as coronary artery luminal stenosis of more than 50%.

Biochemical measurements

Blood samples were drawn following a fasting period of 12 hours. Glucose, creatinine, and lipid profiles were determined by standard methods. The activity of GGT was measured by using an Abbott-Architect autoanalyzer (Abbott-USA) with original kits. CRP was calculated by the nephelometric method (Behring Nephelometer Analyzer, Germany) and expressed as mg/L.

Statistical analysis

Continuous variables were given as mean ± standard deviation (SD). Data were tested for normal distribution using the Shapiro-Wilk test. Groups were compared with the Kruskal-Wallis test for multiple comparisons. When a significant difference between three groups was observed by using the Kruskal-Wallis test, the Mann-Whitney *U*-test was used for the determination of the difference between couples. Correlations between the GGT level and clinical-laboratory variables were assessed by the Pearson's correlation test. Statistical significance was defined as $P < 0.05$. The SPSS statistical software (SPSS for Windows 17.0) was used for all statistical calculations.

Results

The main characteristics of all the study population are reported in table 1. CSX and the control groups were similar by means of demographic features and risk factors (age, gender, smoking history, body mass index, blood pressure and serum glucose and cholesterol levels). However, the CAD group consisted of subjects with older age, male sex dominance and lower HDL cholesterol levels when compared with the control and the CSX groups. Serum GGT activity was higher in the CSX and the CAD groups than in the control group (32.6 ± 16.0 and 30.4 ± 15.3 U/L, respectively, vs. 17.9 ± 4.2 U/L; $P < 0.001$). There was no statistically significant difference in serum GGT activity between the CSX and the CAD groups ($P = 0.67$) (figure 1). When compared with the control group, serum CRP

Table 1. – *Clinical and laboratory parameters in the study groups*

	Control group (n=35)	CSX group (n=40)	CAD group (n=40)	*P* value
Age (year)	52,4 ± 10.6*	51,4 ± 10.6**	60,2 ± 10.9	0.001
Sex (female/male)	24/11¶	21/19¶¶	8/32	< 0.001
Smoker (n)	10	9	13	NS
Body mass index (kg/m^2)	26,8 ± 4.3	27.9 ± 4.0	28.4 ± 4.9	NS
Systolic blood pressure (mm Hg)	123.5 ± 15.0	121.8 ± 12.8	124.5 ± 11.6	NS
Diastolic blood pressure (mm Hg)	73.0 ± 13.5	77.1 ± 10.3	76.3 ± 8.3	NS
Glucose (mg/dL)	98.8 ± 12.2	99.0 ± 13.7	106.0 ± 23.8	NS
Total cholesterol (mg/dL)	191.8 ± 34.4	199.5 ± 40.3	184.0 ± 43.9	NS
LDL-cholesterol (mg/dL)	121.6 ± 26.3	124.1 ± 30.8	116.0 ± 37.9	NS
HDL-cholesterol (mg/dL)	42.3 ± 10.2#	41.5 ± 9.6##	35.7 ± 7.1	0.003
Triglyceride (mg/dL)	140.1 ± 61.8	157.1 ± 61.3	159.7 ± 77.2	NS
Creatinine (mg/dL)	0.78 ± 0.17	0.84 ± 0.15	0.87 ± 0.19	NS
C-reactive protein (mg/L)	2.2 ± 1.8†	4.1 ± 2.0	4.7 ± 2.6	< 0.001
Gamma-glutamyl transferase (U/L)	17.9 ± 4.2∞	32.6 ± 16.0	30.4 ± 15.3	< 0.001
Aspartate aminotransferase (U/L)	22.0 ± 7.7	23.6 ± 9.6	26.9 ± 15.5	NS
Alanine aminotransferase (U/L)	20.0 ± 7.8	24.5 ± 10.6	22.2 ± 9.1	NS
Intima-media thickness (mm)	0.62 ± 0.08ø	0.74 ± 0.17	0.95 ± 0.12øø	< 0.001

*P = 0.004 vs. CAD group; **P = 0.001 vs. CAD; ¶P < 0.001 vs. CAD; ¶¶P = 0.003 vs. CAD; #P = 0.005 vs. CAD; ##P = 0.003 vs. CAD; †P < 0.001 vs. CSX and CAD; ∞P < 0.001 vs. CSX and CAD groups; øP = 0.003 vs. CSX; øøP < 0.001 vs. CSX and control groups.

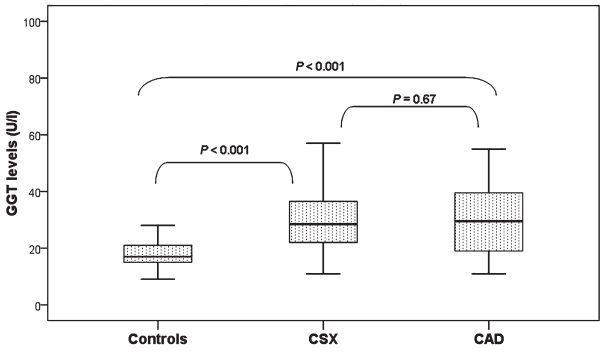

Fig. 1. – Comparison of serum gamma-glutamyl transferase (GGT) levels in all study groups. CAD, coronary artery disease; CSX, cardiac syndrome X.

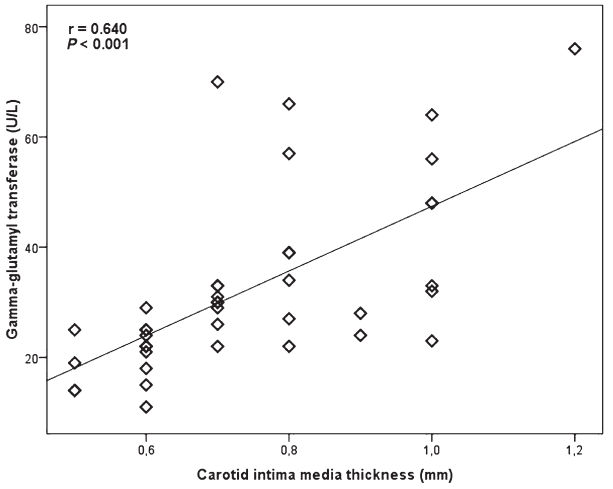

Figure 2. – Relationship between serum gamma-glutamyl transferase activity and carotis intima-media thickness in patients with cardiac syndrome X.

levels were significantly increased in both the CSX and the CAD groups (4.1 ± 2.0 and 4.7 ± 2.6 mg/L, respectively, vs. 2.2 ± 1.8 mg/L; P < 0.001). There was no statistically significant difference in serum CRP levels between the CSX and the CAD groups (P = 0.73). Patients with CSX and CAD had significantly higher CIMT values than the controls (0.74 ± 0.17 and 0.94 ± 0.12 mm, respectively, vs. 0.62 ± 0.08 mm; P < 0.001). A significant correlation was found between GGT activity and CIMT measurements (r = 0.640, P < 0.001) (Figure 2), but serum GGT activity did not correlate with serum CRP levels in patients with CSX (r = 0.277, P > 0.05).

Discussion

In this study, we found that serum GGT activity was significantly increased in patients with CSX as well as in the patients with CAD, when compared with the controls. We also found a strong and significant correlation between serum GGT activity and CIMT.

The pathophysiological mechanisms underlying CSX still remain unclear. Endothelial dysfunction and subangiographic atheroma have been reported in patients with CSX[3]. Abnormal coronary arteries with atheromatous plaques and intimal thickening have also been observed by intravascular ultrasonography studies in patients with CSX[3,13]. Also, the anti-oxidant parameters have been observed to be significantly low in patients with CSX, which supports the reports regarding the oxidative nature of CSX[14,15].

In clinical practice, GGT which is the enzyme responsible for the extracellular catabolism of glutathione[16], is

a commonly used diagnostic test. GGT has an important role in anti-oxidant defense systems. GGT biomarker would fall under a new classification of "oxidative stress" in view of its role in the degradation of the antioxidant glutathione. Decrease in glutathione levels is associated with increased lipid peroxidation, which is an important step in atherosclerotic plaque formation[7,8,17]. There is evidence that GGT is a potential biochemical marker for the preclinical development of atherosclerosis. Paolicchi et al.[11] detected the presence of GGT within the coronary plaque, providing a pathological basis for the hypothesis of the direct participation of GGT in low-density lipoprotein oxidation within the plaque and in atherogenesis and CAD progression. During the last decade, growing evidence has shown that serum GGT is an independent prognostic marker for cardiac death and reinfarction, both in unselected populations and in patients with CAD. In their prospective study, Ruttmann and colleagues have found a strong association between high GGT levels and cardiovascular mortality, which suggests that a high GGT level is an independent risk factor for cardiovascular disease[18]. A recently performed study, LURIC, has shown that serum GGT is predictive of all-cause and cardiovascular mortality in individuals with CAD, independently of other cardiovascular risk factors[19]. In our study, we detected GGT levels higher in patients with CSX similar to patients with CAD than the controls. Therefore, we speculated that GGT might play a role in the pathogenesis of microvascular atherosclerosis in CSX.

CIMT is measured noninvasively by ultrasonography and is a widely accepted marker of atherosclerosis. Increased CIMT represents an early phase of the atherosclerotic process[20-22]. In previous studies, increased CIMT was found in CSX patients despite angiographically normal coronary arteries[23,24]. This finding confirms the reports of Cox et al.[3] and others[13] regarding the presence of subangiographic atheroma in CSX patients and, emphasizes the limitations of coronary angiography to detect early signs of atherosclerosis, such as intima media thickening. We also found that CIMT was increased in patients with CSX in comparison with the controls, although both groups had similar risk factors for CAD. Also there was a significant correlation between CIMT and GGT. This finding may support the role of GGT in the early atherosclerotic process in CSX patients.

Another finding of our study is that we detected increased CRP levels in CSX patients compared with the controls. This finding supports the results of the previous studies, which have observed increased CRP levels in CSX patients[23,25,26]. However, we did not detect a relationship between GGT and CRP in patients with CSX, which allows a hypothesis that these biomarkers may be associated with different specific pathogenetic aspects of the atherosclerotic process. Increased GGT levels independent from serum CRP levels may contribute to the early atherosclerotic process of CSX.

The major limitation of our study is the smaller number of the study population. Also, despite the superiority of the ergonovine test to the hyperventilation test, we preferred to use the hyperventilation test instead of the ergonovine injection to rule out coronary vasospasm in patients with CSX, because of the possibility of persistent, severe and painful spasm with ergonovine.

In conclusion, in our study, patients with CSX had higher plasma GGT levels similar to CAD patients than the controls. Also, we showed a strong correlation between GGT and increased CIMT in CSX patients. These findings suggest that an increased GGT level may play a role in the pathogenesis of the microvascular atherosclerotic process of CSX.

To our knowledge, this is the first study to report an association between increased serum GGT activity and CSX. Further investigation of the role of serum GGT activity in the pathogenesis of CSX is needed.

Conflict of interest: none declared.

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