

# Comparison of serum gamma-glutamyltransferase levels between patients with cardiac syndrome X and healthy asymptomatic individuals

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## Abstract

**Background:** Gamma-glutamyltransferase (GGT) enzyme has an increasing importance in the pathophysiology and prognosis of cardiovascular diseases. It is an indirect marker of microvascular endothelial dysfunction, atherosclerosis, and elevated oxidative stress. There are no adequate data on the relationship between GGT and cardiac syndrome X.

**Aim:** To compare serum GGT levels between patients with cardiac syndrome X and asymptomatic healthy individuals.

**Methods:** Fifty consecutive patients (29 female, 21 male, aged 28–81 years) who underwent coronary angiography due to objective ischaemia and were eventually diagnosed with cardiac syndrome X between July 2009 and January 2010, and 50 healthy asymptomatic control individuals (28 female, 22 male, aged 30–78 years) were studied. Venous blood samples were collected for GGT measurements. A metabolic syndrome (MS) subgroup composed of 15 individuals was formed within the cardiac syndrome X group.

**Results:** Serum total cholesterol, LDL-cholesterol, and triglyceride (TG) levels were significantly higher in the cardiac syndrome X patients than in the control group ( $195.28 \pm 33.71$  mg/dL and  $168.82 \pm 31.45$  mg/dL,  $p < 0.01$ ,  $121.62 \pm 30.53$  mg/dL and  $98.44 \pm 27.28$  mg/dL,  $p < 0.01$ ,  $144.30 \pm 68.54$  mg/dL and  $108.94 \pm 43.59$  mg/dL,  $p < 0.01$ , respectively). Serum GGT levels were also significantly higher in the cardiac syndrome X patients than in the control group ( $30.48 \pm 16.36$  and  $17.88 \pm 6.89$  U/L,  $p < 0.001$ ). The MS patients ( $n = 15$ ) had significantly higher TG and GGT levels ( $230.00 \pm 41.37$  mg/dL and  $107.57 \pm 37.90$  mg/dL,  $p < 0.01$ ,  $38.47 \pm 21.27$  U/L and  $27.06 \pm 12.61$  U/L,  $p < 0.001$ , respectively) and lower HDL levels ( $35.47 \pm 6.91$  mg/dL and  $48.26 \pm 9.97$  mg/dL,  $p < 0.05$ ) compared to patients without MS. The cardiac syndrome X group exhibited a significant positive correlation between GGT and body mass index, and GGT and TG ( $r = 0.321$ ,  $p = 0.023$ ,  $r = 0.293$ ,  $p = 0.039$ , respectively).

**Conclusions:** GGT activity in patients with cardiac syndrome X was higher than in healthy controls. Moreover, GGT activity was further increased in those patients with cardiac syndrome X who had also MS.

**Key words:** cardiac syndrome X, gamma-glutamyltransferase, oxidative stress

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## INTRODUCTION

Coronary artery disease (CAD) is the commonest cause of death worldwide [1]. Coronary angiography is a common method for diagnosing CAD. However, 10–30% of patients undergoing coronary angiography because of chest pain de-

monstrate normal coronary arteries [2]. These patients with angina and ischaemia during stress testing are termed 'cardiac syndrome X' [3]. Although long-term prognosis appears to be good, recurrent chest pain leads to a considerable rate of morbidity. Therefore, the physiopathology of cardiac syn-

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drome X should be revealed in a clear fashion and the treatment options for those patients should be further developed.

The pathogenesis of cardiac syndrome X has not been clearly outlined. Although various theories have been proposed involving different mechanisms, microvascular dysfunction is regarded as the most widely recognised underlying reason [4]. Elevated oxidative stress is one of the important conditions that can lead to endothelial dysfunction [5].

Gamma-glutamyltransferase (GGT) is an enzyme which is present in the cell membranes of many tissues and acts as a mediator in the transmembrane transfer of glutathione, a significant component of intracellular antioxidant protective mechanisms. Considerable advances have been made in understanding the physiological roles and cellular effects of GGT. The importance of the oxidative stress — GGT relationship has been well understood [6]. Prospective epidemiological studies, showed that the risk for development of type 2 diabetes mellitus (DM) [7], metabolic syndrome (MS) [8], and CAD [9] is increased with elevated GGT levels in the general population.

Moreover, GGT has been demonstrated to be a predictor of total mortality and cardiovascular (CV) mortality independent of the classical CV risk factors in CAD [10]. Recently, Breitling et al. [11] followed patients with stable CAD for eight years and confirmed the prognostic importance of GGT as a predictor independent of traditional CV risk factors. Mason et al. [12] described GGT as a novel CV marker. The close relationship of GGT with CV events can be explained by the fact that GGT is a biomarker indicating oxidative stress and is also a proatherogenic marker indirectly related with the biochemical steps of LDL oxidation.

Although the relationship between serum GGT levels and many diseases has been investigated [7–9], no conclusive evidence for such a relationship in cardiac syndrome X has been shown. Therefore, in our study, we aimed to compare the serum GGT levels between cardiac syndrome X patients and healthy individuals, as a marker of microvascular endothelial dysfunction, microvascular atherosclerosis, and elevated oxidative stress.

## METHODS

We enrolled a total of 100 subjects: 50 patients who had undergone coronary angiography due to objective ischaemia and eventually been diagnosed with cardiac syndrome X between July 2009 and January 2010, and 50 healthy asymptomatic control individuals.

### Patients

Cardiac syndrome X diagnosis was based on [13]: (1) typical exercise-induced angina (with or without additional resting angina and dyspnoea); (2) positive exercise stress ECG (ET) or other stress imaging modality; and (3) angiographically normal coronary arteries.

Patients with the following were excluded from the study: CAD, hypertension, heart failure, valvular heart disease,

atrial fibrillation, left bundle branch block, myocarditis, gall bladder and biliary tract diseases, acute and chronic hepatitis, alcoholic liver disease,  $\geq 30$  g daily alcohol consumption, malignancy, use of angiotensin converting enzyme inhibitors and angiotensin receptor blockers, use of statins or fibric acid derivative drugs, use of hepatotoxic drugs, vasospastic angina, chest pain associated with reasons other than cardiac origin, DM or abnormal fasting glucose levels.

Our study was approved by the local ethics committee. Informed consent was obtained from each patient in the study.

Angina classification was carried out according to the Canadian Cardiovascular Society grading of angina pectoris [14]. In this study, ET or myocardial perfusion scintigraphy was used for the detection of objective ischaemia signs.

Controls: These subjects were not diabetic or hypertensive and had no angina or equivalent complaints, while having a ten-year CV risk below 10% based on Framingham risk score and showing no ischaemia in ET [15]. Since ischaemia presence was excluded in each control by ET, coronary angiography was not performed.

Nearly all the patients enrolled in the study received transthoracic echocardiography in order to exclude structural heart disease. Liver function tests were applied in all our patients and AST, ALT, AP, and GGT levels were evaluated. In cases exhibiting elevated values in these tests, hepatobiliary ultrasonography was performed to exclude any case of hepatobiliary disease. Moreover, patients who had right upper quadrant pain, swelling, dyspeptic complaints, or reflective back pain, were also subjected to hepatobiliary ultrasonography. Patients with a hepatobiliary abnormality were excluded from the study. Patients with normal liver test results and cases having no symptoms suggestive of hepatobiliary disease were not subjected to hepatobiliary ultrasonography.

### Exercise stress test

Twenty-nine patients underwent ET using modified Bruce protocol. Exercise stress test was defined positive in the presence of at least 1 mm horizontal or downsloping ST segment depression in at least two derivations and 60–80 ms after J point. After reaching the heart rate corresponding to the patient's age, or following development of the symptom, ET was ended. Symptoms during exercise and the maximum stress capacity were recorded. Duke treadmill score was calculated in each patient after ET [16]. Patients with a Duke treadmill score  $\leq 4$  were recognised as moderate- or high-risk patients and included in the study. Those with a Duke treadmill score  $\geq 5$  were defined as low-risk patients and were not subjected to coronary angiography.

### Myocardial perfusion scintigraphy

We applied myocardial perfusion scintigraphy using Tc-99m MIBI in 21 patients, of whom six received it due to failure to assess ECG changes because of ST depression  $> 1$  mm, and 15 received it due to inconclusive ET, indefinite diagnosis,

and low exercise tolerance levels. Reversible perfusion defects were regarded as ischaemia.

### Coronary angiography

Coronary angiography was performed via the right femoral artery by the Judkins technique (Siemens Axiom 2003, Siemens Bior 2002, and Toshiba 2004). Two experienced cardiologists blinded to the clinical data evaluated the coronary angiography results. Normal coronary artery was defined as absence of any mural irregularity. Coronary artery disease was defined as presence of a > 20% stenosis in any of the large coronary arteries including the large diagonal and obtuse marginal branches. Patients with a coronary angiography showing mural irregularity, but displaying no stenosis higher than 20%, were thought to be likely to have atheroma plaques and excluded from the study. Coronary artery vasospasm was excluded by applying a hyperventilation test.

### Laboratory parameters

Venous blood specimens were collected from the patients following a fasting period of 12 h. Serum glucose levels were studied using the enzymatic colorimetric method, whereas creatinine was measured by Jaffe assay and urea by the coupled enzymatic method; AST, ALT, and ALP levels were analysed by the enzymatic colorimetric method; GGT was evaluated by the enzymatic colorimetric method with the Roche/Hitachi kit. While total cholesterol level was determined by the enzymatic colorimetric method (trinder reaction), HDL was measured by homogeneous enzymatic colorimetric assay and triglycerides (TG) was assessed by the enzymatic colorimetric method. VLDL cholesterol level was calculated using the following formula:  $VLDL = TG/5$ . LDL cholesterol level was calculated by the Friedewald formula among individuals with a TG level below 400 mg/dL [17]. Waist circumference was measured by a tape line parallel to the ground from the narrowest distance between the lowest rib and processus spina iliaca anterior. Body mass index (BMI) was calculated by the following formula:  $mass [kg]/height [m]^2$ .

### Metabolic syndrome subgroup

Metabolic syndrome was defined based on the diagnostic guidelines of the National Cholesterol Education Program — Adult Treatment Panel (NCEP ATP) III [18]. However, since patients with impaired fasting glucose and hypertension were excluded, MS diagnosis was established in the presence of at least three of the following criteria: waist circumference > 102 cm in men and > 88 cm in women; HDL level < 40 mg/dL in men and < 50 mg/dL in women; TG level  $\geq$  150 mg/dL; and systolic blood pressure  $\geq$  130 or < 140 mm Hg, or diastolic blood pressure  $\geq$  85 or < 90 mm Hg.

### Statistical analysis

Acquired data was analysed using SPSS 15.0. Continuous variables are expressed as mean  $\pm$  SD. Intergroup differ-

ences were evaluated by Mann-Whitney U test. Kolmogorov-Smirnov test was used for testing normal distribution of the data. Correlations were evaluated by Pearson correlation test. A p value < 0.05 was regarded as significant.

## RESULTS

In the cardiac syndrome X group, 29 patients were female and mean age was  $51.04 \pm 10$  years. In the control group, 28 were female and mean age was  $50.91 \pm 11$  years. General demographic characteristics of the patients are shown in Table 1. There was no difference between the two groups in terms of age, gender or smoking status. Waist circumference and BMI were significantly higher in the cardiac syndrome X group than in the control group.

No difference was found between the two groups with regard to fasting plasma glucose, urea, or creatinine values. Serum total cholesterol, LDL, and TG levels were significantly higher in syndrome X patients than in controls. There was no difference between the two groups in terms of HDL. While no difference was found between the groups with regard to serum AST, ALT, or ALP levels, the cardiac syndrome X group demonstrated significantly higher serum GGT levels compared to controls.

A significant positive correlation between GGT and BMI, and GGT and TG was found in the cardiac syndrome X group (Table 2).

When patients with or without MS were compared, TG concentration was statistically significantly higher in the MS group, whereas HDL was lower in the MS group. Serum AST, ALT, and ALP levels were similar, whereas GGT was significantly higher in the MS group (Table 3).

## DISCUSSION

In this study, we reached two important conclusions: (1) GGT activity increases in cardiac syndrome X patients; and (2) the presence of MS further increases GGT activity. Microvascular endothelial dysfunction due to elevated oxidative stress in cardiac syndrome X patients is one of the mechanisms explaining the pathophysiology of the disease [4]. Oxidative stress is thought to cause a reduction in glutathione concentration (an antioxidant molecule), which in turn is believed to stimulate GGT activity [19, 20]. Therefore, elevated GGT activity in cardiac syndrome X patients may be a result of increased oxidative stress. While it has been shown that some treatments can reduce oxidative stress in cardiac syndrome X cases, there is no strong evidence suggestive of an elevation in oxidative stress in this patient population. Further studies are required in this field [4].

Similarly it has been shown that, serum GGT level is elevated in patients with coronary slow flow phenomenon, probably caused by microvascular and endothelial dysfunction [21]. Diffuse atherosclerosis has been shown to cause microvascular resistance in slow flow phenomenon by intravascular ultrasonography (IVUS) and fractional flow reserve [22, 23].

**Table 1.** Comparison of demographic and laboratory data between cardiac syndrome X patient and controls

	Cardiac syndrome X group	Control group	P
Number of patients	50	50	
Age [years]	51.04 ± 10.11	50.91 ± 11.03	NS
Gender (female/male)	29/21	28/22	NS
Smoking [%]	18	16	NS
Waist circumference [cm]	96.74 ± 11.42	86.90 ± 8.43	< 0.01
Body mass index [kg/m <sup>2</sup> ]	29.43 ± 6.19	25.20 ± 3.56	< 0.01
Urea [mg/dL]	30.36 ± 7.20	29.12 ± 7.44	NS
Creatinine [mg/dL]	0.76 ± 0.12	0.73 ± 0.11	NS
Fasting plasma glucose [mg/dL]	93.26 ± 5.72	91.24 ± 6.22	NS
Total cholesterol [mg/dL]	195.28 ± 33.71	168.82 ± 31.45	< 0.01
Low-density lipoprotein [mg/dL]	121.62 ± 30.53	98.44 ± 27.28	< 0.01
High-density lipoprotein [mg/dL]	44.42 ± 10.85	46.22 ± 10.93	NS
Triglyceride [mg/dL]	144.30 ± 68.54	108.94 ± 43.59	< 0.01
Aspartate transaminase [U/L]	20.86 ± 5.57	19.68 ± 4.94	NS
Alanine transaminase [U/L]	20.94 ± 8.64	20.24 ± 9.97	NS
Alkaline phosphatase [U/L]	67.72 ± 19.24	72.16 ± 16.43	NS
Gamma-glutamyltransferase [U/L]	30.48 ± 16.36	17.88 ± 6.89	< 0.001

**Table 2.** Correlation between gamma-glutamyltransferase (GGT) and lipid profile, body mass index (BMI), and waist circumference (WC)

	Control group			Cardiac syndrome X group		
	n	r	p	n	r	p
BMI GGT	50	-0.019	0.898	50	0.321	0.023
WC GGT	50	-0.084	0.561	50	0.276	0.052
TC GGT	50	0.092	0.525	50	-0.032	0.826
LDL GGT	50	0.129	0.372	50	-0.126	0.381
HDL GGT	50	-0.073	0.613	50	0.024	0.867
TG GGT	50	0.150	0.299	50	0.293	0.039

TC — total cholesterol; TG — triglyceride; LDL — low-density lipoprotein; HDL — high-density lipoprotein

**Table 3.** Comparison of laboratory values between patients with cardiac syndrome X with or without metabolic syndrome (MS)

	Cardiac syndrome X group		P
	MS (+) (n = 15)	MS (-) (n = 35)	
Total cholesterol [mg/dL]	202.07 ± 22.83	198.09 ± 35.29	NS
Low-density lipoprotein [mg/dL]	131.33 ± 23.41	127.46 ± 22.53	NS
High-density lipoprotein [mg/dL]	35.47 ± 6.91	48.26 ± 9.97	< 0.05
Triglyceride [mg/dL]	230.00 ± 41.37	107.57 ± 37.90	< 0.001
Aspartate transaminase [U/L]	20.34 ± 5.45	19.83 ± 4.91	NS
Alanine transaminase [U/L]	20.67 ± 7.14	20.29 ± 8.87	NS
Alkaline phosphatase [U/L]	68.42 ± 19.74	70.16 ± 17.33	NS
Gamma-glutamyltransferase [U/L]	38.47 ± 21.27	27.06 ± 12.61	< 0.001

Therefore, atherosclerosis, which often accompanies slow flow phenomenon, may trigger serum GGT activity by further raising the oxidative stress.

Despite excluding two major diagnostic criteria of MS, namely diabetes or impaired fasting glucose and hypertension, cardiac syndrome X patients with MS demonstrated higher GGT levels compared to cardiac syndrome X patients without MS. This finding supports a strong relationship between MS and GGT. The higher increase of GGT activity in the MS subgroup than in those without MS may imply that MS risk factors induce higher GGT activity. Although elevated GGT activity in cardiac syndrome X patients is a finding supportive of raised oxidative stress, oxidative stress may not increase as much as in CAD, DM, or MS which encompasses more than one risk factor. Moreover, the positive correlation between GGT and BMI, and GGT and TG may be associated with MS and the risk of MS development.

Kawamoto et al. [8] compared the serum GGT levels of a normal population and a group of MS patients. They demonstrated higher GGT levels in the MS group and explained this finding by insulin resistance. Another study found that elevated serum GGT levels raised the likelihood of MS development within the following four years [24]. Similarly, in the TEKHARF study [25], the close relationship between GGT and MS was confirmed.

While coronary angiography can provide lumen images created by the contrast agent, it cannot completely visualise eccentrically localised lesions and supply adequate information on the size and composition of an atheromatous plaque [26]. Performing IVUS in patients with a coronary artery that appears to be normal usually reveals atherosclerosis [27]. Therefore, the absence of atherosclerosis cannot be completely excluded by coronary angiography in cardiac syndrome X.

In other words, cardiac syndrome X may have a concurrent microvascular atherosclerosis or diffuse atherosclerosis that cannot be visualised by coronary angiography. This accompanying atherosclerosis may also raise the GGT activity.

### Limitations of the study

The low number of overall patients, the relatively small size of the MS subgroup within the cardiac syndrome X group, and the lack of screening for asymptomatic hepatobiliary diseases and fatty liver by abdominal ultrasonography in all the patients, can all be mentioned as limitations of our study. As is well-known, inflammation plays a role in the development of MS as well as in atherosclerosis [28]. Failing to evaluate C-reactive protein level, an important indicator of inflammation, in the MS and cardiac syndrome X groups may be considered as one of the other limitations of the current study.

Moreover, the absence of endothelial function analysis by flow-mediated dilation and failure to evaluate the relationship between GGT and nitric oxide-related substances such as asymmetric dimethyl arginine and markers such as

total antioxidant capacity which can be associated with endothelial dysfunction and elevated oxidative stress, may be considered major limitations of our study.

### CONCLUSIONS

Raised plasma GGT levels were shown in a cardiac syndrome X group. Further studies with larger series are required in order to reveal the complete pathophysiological role of GGT in cardiac syndrome X patients.

**Conflict of interest:** none declared

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# Porównanie stężeń gamma-glutamylotransferazy w surowicy między chorymi z sercowym zespołem X i zdrowymi osobami bez objawów

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## Streszczenie

**Wstęp:** Gamma-glutamylotransferaza (GGT) jest enzymem, któremu przypisuje się coraz większe znaczenie w patofizjologii i ocenie ryzyka chorób sercowo-naczyniowych. Mimo to brakuje odpowiednich danych na temat zależności między aktywnością GGT a sercowym zespołem X.

**Cel:** Celem pracy było porównanie stężeń GGT w surowicy chorych z sercowym zespołem X i zdrowych osób bez objawów, jako pośredniego markera dysfunkcji śródbłonna w mikrokrążeniu, miażdżycy i zwiększonego stresu oksydacyjnego.

**Metody:** Do badania włączono łącznie 100 osób, w tym 50 kolejnych chorych (29 kobiet i 21 mężczyzn w wieku 28–81 lat), u których wykonano koronarografię z powodu obiektywnych objawów niedokrwienia mięśnia sercowego i u których rozpoznano sercowy zespół X w okresie od lipca 2009 do stycznia 2010 r. oraz 50 zdrowych osób bez objawów, stanowiących grupę kontrolną (28 kobiet i 22 mężczyzn w wieku 30–78 lat). Analizie poddano próbki krwi żyłnej pobrane od uczestników badania po upływie 12 godzin od ostatniego posiłku. Stężenie GGT oznaczano metodą kolorymetryczną. Spośród pacjentów z sercowym zespołem X wydzielono 15-osobową grupę spełniającą kryteria zespołu metabolicznego wg NCEP ATP III.

**Wyniki:** Stężenia cholesterolu całkowitego, cholesterolu frakcji LDL i triglicerydów były istotnie wyższe u chorych z sercowym zespołem X niż u osób z grupy kontrolnej (odpowiednio  $195,28 \pm 33,71$  mg/dl i  $168,82 \pm 31,45$  mg/dl;  $p < 0,01$ ;  $121,62 \pm 30,53$  mg/dl i  $98,44 \pm 27,28$  mg/dl;  $p < 0,01$ ;  $144,30 \pm 68,54$  mg/dl i  $108,94 \pm 43,59$  mg/dl;  $p < 0,01$ ). Również stężenia GGT w osoczu były istotnie wyższe u chorych z sercowym zespołem X (odpowiednio  $30,48 \pm 16,36$  i  $17,88 \pm 6,89$  j./l.;  $p < 0,001$ ). W wydzielonej spośród chorych z sercowym zespołem X podgrupie osób spełniających kryteria zespołu metabolicznego ( $n = 15$ ) stwierdzono istotnie wyższe stężenia triglicerydów i GGT ( $230,00 \pm 41,37$  mg/dl i  $107,57 \pm 37,90$  mg/dl;  $p < 0,01$ ;  $38,47 \pm 21,27$  i  $27,06 \pm 12,61$  j./l.;  $p < 0,001$ ) oraz niższe stężenia cholesterolu frakcji HDL (odpowiednio  $35,47 \pm 6,91$  mg/dl i  $48,26 \pm 9,97$  mg/dl;  $p < 0,05$ ) w porównaniu z pacjentami z sercowym zespołem X bez zespołu metabolicznego. W grupie osób z sercowym zespołem X wykazano statystycznie istotną dodatnią korelację między stężeniem GGT i wskaźnikiem masy ciała oraz między stężeniami GGT i triglicerydów (odpowiednio  $r = 0,321$ ;  $p = 0,023$  i  $r = 0,293$ ;  $p = 0,039$ ).

**Wnioski:** W niniejszym badaniu u chorych z sercowym zespołem X aktywność GGT była większa niż u osób z grupy kontrolnej. Ponadto wykazano, że zespół metaboliczny wiązał się z dalszym wzrostem aktywności GGT u pacjentów z sercowym zespołem X.

**Słowa kluczowe:** sercowy zespół X, gamma-glutamylotransferaza, stres oksydacyjny

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