Is there any relationship between serum γ-glutamyltransferase levels and premature coronary artery disease?

Czy istnieje związek między stężeniem γ-glutamylotransferazy a przedwczesną chorobą wieńcową?

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Postep Kardiol Inter 2012; 8, 2 (28): 96–101
DOI: 10.5114/pwki.2012.29650

Abstract

Background: The relationship between γ-glutamyltransferase (GGT) and coronary artery disease (CAD) has been revealed in several previous studies. However, the relationship between the severity of CAD and GGT levels has not been previously studied in a premature group (< 40 years old).

Aim: We aim to investigate whether GGT is associated with premature CAD.

Material and methods: The study population consisted of 181 premature coronary artery disease patients (group 1; mean age: 36.5 ±2.5 years) and 80 controls (group 2; mean age: 37.2 ±2.3 years). The severity of CAD in group 1 was evaluated by the Gensini scoring system. γ-Glutamyltransferase levels and the other basic biochemical parameters were analyzed, and relations with severity of CAD were evaluated.

Results: There were no statistically significant differences in serum GGT activity between the two groups ($p > 0.05$). γ-Glutamyltransferase levels in group 1 were found not to be correlated with the severity of premature CAD ($r = –0.016$, $p = 0.828$). Furthermore, in subgroup analyses we found glycated hemoglobin (HbA_{1c}) levels significantly correlated with the severity of CAD in diabetic premature CAD patients, but not GGT ($r = 0.448$, $p < 0.001$; $r = 0.157$, $p = 0.127$, respectively).

Conclusions: γ-Glutamyltransferase level was not associated with severity of CAD in the premature group. Possibly, there is no predictive importance of GGT in patients with premature CAD.

Key words: γ-glutamyltransferase, premature, coronary artery disease, Gensini score

Streszczenie

Wstęp: W kilku opublikowanych wcześniej badaniach wykazano związek między γ-glutamylotransferazą (GGT) i chorobą wieńcową (*coronary artery disease* – CAD). Mimo to nie analizowano dotychczas związku między zaawansowaniem CAD a stężeniem GGT w grupie młodych pacjentów (< 40. roku życia).

Cel: Ustalenie, czy stężenie GGT wiąże się z zaawansowaniem przedwczesnej CAD.

Materiał i metody: Przebadano grupę 181 pacjentów z przedwczesną CAD (grupa 1.; średni wiek: 36,5 ±2,5 roku) oraz 80 osób z grupy kontrolnej (grupa 2.; średni wiek: 37,2 ±2,3 roku). Zaawansowanie CAD w grupie 1. oszacowano na podstawie skali Gensiniego. Oznaczono stężenie GGT oraz innych podstawowych parametrów biochemicznych oraz przeanalizowano ich związek z zaawansowaniem CAD.

Wyniki: Nie obserwowano istotnych różnic w aktywności GGT w surowicy między obiema grupami ($p > 0,05$). W grupie 1. stężenie GGT nie korelowało z zaawansowaniem przedwczesnej CAD ($r = –0,016$, $p = 0,828$). Analiza podgrup wykazała ponadto, że u pacjentów z cukrzycą i przedwczesną CAD poziom HbA_{1c}, ale nie GGT, istotnie korelował z zaawansowaniem CAD (odpowiednio $r = 0,448$, $p < 0,001$; $r = 0,157$, $p = 0,127$).

Wnioski: Stężenie GGT nie było związane z zaawansowaniem przedwczesnej CAD. γ-Glutamylotransferaza nie ma prawdopodobnie znaczenia predykcyjnego u pacjentów z przedwczesną CAD.

Słowa kluczowe: γ-glutamylotransferaza, choroba wieńcowa, skala Gensiniego

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Praca wpłynęła: 6.03.2012, **przyjęta do druku:** 28.05.2012.

Introduction

Coronary artery disease (CAD) began to be observed in younger ages especially in developing countries [1]. As known, the process of atherosclerosis begins from very early ages as fatty streaks [2]. Although genetic predisposition is usually accused of the accelerated atherosclerosis and premature coronary artery disease, the exact mechanism is not fully known. Also, there are publications showing that oxidative stress may play a role in premature atherosclerosis [3, 4].

γ-Glutamyltransferase (GGT) is a biomarker which is mostly used for the detection of liver diseases and alcohol consumption. Also, it has an important role in the degradation of glutathione extracellularly. Glutathione is an antioxidant molecule against reactive oxygen species. Thus, GGT is accepted to be a pro-oxidant molecule. Oxidative stress was shown to play important roles in many phases of atherosclerosis [3]. Elevated serum GGT levels have been shown to be associated with development of diabetes mellitus (DM), hypertension (HT) and metabolic syndrome [5-7]. The relationship between GGT levels and CAD is established in many studies [8-10]. However, there is only one study investigating GGT levels in premature coronary artery disease, but in limited circumstances [11].

Aim

In this study, we hypothesized that oxidative stress may have a role in premature atherosclerosis and pro-oxidant function of GGT may be related to premature CAD. Therefore, we aimed to investigate whether GGT is associated with premature coronary artery disease.

Material and methods

Study population

The study population consisted of 181 premature coronary atherosclerotic patients (group 1; mean age: 36.5 ±2.5 years) and 80 control subjects (group 2; mean age: 37.2 ±2.3 years) selected from 3625 patients who had undergone coronary angiography at 2 different study centers (Abant Izzet Baysal University School of Medicine Hospital and Sivas Numune Hospital) between January 2010 and December 2011. The control group consisted of 80 patients, age-matched and sex-matched individuals, who were selected in a consecutive manner from the catheterized patients during the same study period and who proved to have normal coronary angiograms. Demographic parameters, risk factors for atherosclerosis and past medical history were recorded for all patients.

Hypertension was considered to be present if the systolic pressure was greater than 140 mm Hg and/or diastolic pressure was greater than 90 mm Hg, or if the individual was taking antihypertensive medications. Diabetes was defined as fasting blood sugar greater than 126 mg/dl or current use of diet or medication to lower blood glucose. Cigarette smoking was defined as use of more than 10 cigarettes/day at the time of diagnosis. Subjects with a history of percutaneous transluminal coronary angioplasty, acute myocardial infarction, alcohol consumption, antioxidant drug use, renal or hepatic insufficiency and type 1 DM were excluded from the study. The indication for coronary angiography was either the presence of typical angina or positive or equivocal results of noninvasive screening tests for myocardial ischemia, in all groups. The study protocol was approved by the local ethics committee and informed consent was obtained from all patients.

Coronary angiography

Coronary angiography was performed by the Judkin's technique. Two experienced cardiologists who were blinded to the patients' data analyzed the angiographic results. All angiograms were evaluated by the Gensini scoring system in terms of severity of coronary stenosis in group 1. A score of 1 indicates 1-25%, 2 indicates 26-50%, 4 indicates 51-71%, 8 indicates 76-90%, and 16 indicates 91-99% narrowing of the lumen of the coronary artery, and a score of 32 indicates a totally occluded artery. The Gensini score is multiplied by a factor which is associated with the functional importance of the coronary artery depending on the myocardial region supplied by that coronary segment. This factor is 5 for left main system lesions, 2.5 for proximal left anterior descending artery and proximal circumflex artery lesions, 1 for distal left anterior descending artery, mid/distal circumflex artery and right coronary artery lesions, and 0.5 for lesions in any other artery branches [12].

Biochemical investigations

Blood samples were obtained after overnight fasting (at least 12 h) for analysis of transaminases, creatinine, total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), hemoglobin, and glucose with standard methods. The activity of GGT was measured using an Abbott-Architect autoanalyzer with original kits (Abbott Laboratories, CA, USA).

Statistical analysis

All statistical analyses were performed using the SPSS software package 15.0 (SPSS Inc, Chicago, IL, USA). Data are presented as frequencies and percentages for categorical variables and mean ± SD or median for continuous variables, unless otherwise indicated. The groups were compared using Student's *t*-test for continuous variables and the χ^2 test for categorical variables. Correlation between continuous variables was determined by Pearson correlation coefficients. Binary logistic regression analysis was performed to identify the independent predictors of severe CAD. A value of $p < 0.05$ was considered statistically significant.

Results

There were no statistically significant differences between the groups (group 1 and 2) with respect to hypertension and diabetes mellitus, and smoking ($p > 0.05$). Laboratory characteristics of groups were not statistically different. The main clinical characteristics of both groups are shown in Table 1. There were no statistically significant differences in serum GGT activity between the groups ($p = 0.483$).

In subgroup analyses of group 1, 97 patients had mild CAD (Gensini score ≤ 20), 84 patients had moderate-high CAD (Gensini score > 28). All patients were younger than 40 years of age. There were no significant differences in age, DM, HT, family history, creatinine levels, or smoking between groups (Table 2). Also, GGT and glycated hemoglobin (HbA_{1c}) values were not statistically different between groups; furthermore, they were not found to be correlated with Gensini score.

However, other subgroup analysis was done in diabetic premature CAD patients and it showed a significant correlation between HbA_{1c} and Gensini score ($r = 0.448$, $p < 0.001$; Figure 1). Gensini score was significantly higher ($p < 0.001$) in diabetic patients than non-diabetics. γ-Glutamyltransferase values were significantly higher ($p = 0.003$) in diabetic patients than non-diabetics. But, there was no correlation between GGT and Gensini score in diabetic patients, as in the whole population ($r = 0.157$, $p = 0.127$).

In linear multivariate regression analysis (including age, GGT levels, HbA_{1c} levels, smoking and HT as dependent parameters) for Gensini score, independent parameters for Gensini score in non-diabetic patients could not be found. However, HbA_{1c} levels and HT emerged as significant independent determinants in diabetic patients

Table 1. Clinical and laboratory parameters in the study groups
Tabela 1. *Parametry kliniczne i laboratoryjne w badanych grupach*

Parameter	CAD group ($n = 181$)	Control ($n = 81$)	Value of p
Male/female	158/23	70/11	0.846
Age [years]	36.5 ±2.5	36.5 ±2.7	0.920
Systemic hypertension [%]	13.8	14.4	0.441
Diabetes mellitus [%]	12.4	12.5	0.803
Smokers [%]	38.8	35.5	0.935
Hemoglobin [g/dl]	13.8 ±1.55	13.4 ±1.32	0.827
Total cholesterol [mg/dl]	176.5 ±33.7	178 ±34.5	0.266
LDL cholesterol [mg/dl]	102 ±26.2	98 ±24.6	0.284
HDL cholesterol [mg/dl]	44.2 ±11.4	44.8 ±10.6	0.822
Triglycerides [mg/dl]	129.2 ±31.8	132.3 ±34.7	0.808
Creatinine [mg/dl]	0.71 ±0.18	0.73 ±0.13	0.449
Statin [%]	8.4	7.9	0.801
AST [U/l]	22.5 ±6.6	21.9 ±6.4	0.852
ALT [U/l]	23.0 ±5.6	22.8 ±5.8	0.833
GGT [U/l]	37.8 ±13.0	36.8 ±9.0	0.483
ALP [U/l]	156.4 ±55.6	153.3 ±51.3	0.785
Direct bilirubin [mg/dl]	0.2 ±0.1	0.2 ±0.1	0.867

ALT – alanine aminotransferase, ALP – alkaline phosphatase, AST – aspartate aminotransferase, CAD – coronary artery disease, CAE – coronary artery ectasia, GGT – γ-glutamyltransferase, HDL – high-density lipoprotein, LDL – low-density lipoprotein

Table 2. Demographic and clinical variables of the patients with CAD according to Gensini score
Tabela 2. *Zmienne demograficzne i kliniczne u pacjentów z CAD w zależności od wskaźnika Gensiniego*

Parameter	Gensini score ≤ 20 ($n = 97$)	Gensini score > 20 ($n = 84$)	Value of p
Age [years]	36.2 ±2.5	37.0 ±2.4	0.052
Gender (male/female)	95/2	63/21	0.003
HT [%]	32.7	46.1	0.065
BMI [kg/m^2]	27.1 ±4.2	27.6 ±4.3	0.352
Smokers [%]	50.5	58.2	0.288
DM [%]	30.7	31.1	0.412
HbA_{1c} [%]	6.6 ±1.7	6.7 ±1.4	0.526
GGT	36.8 ±13.4	37.2 ±12.7	0.414
Glucose [mg/dl]	144.9 ±59.5	148.3 ±74.5	0.477
Creatinine [mg/dl]	1.02 ±0.24	1.05 ±0.29	0.203

DM – diabetes mellitus, HT – hypertension, GGT – γ-glutamyltransferase, BMI – body mass index

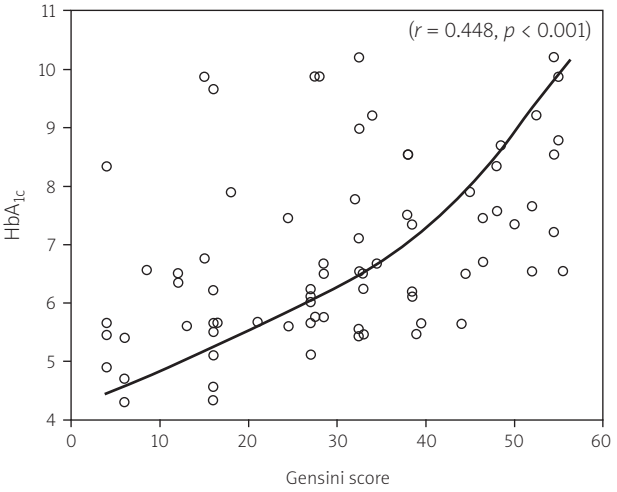

Fig. 1. Correlation between HbA_{1c} and Gensini score in diabetic premature CAD patients
Ryc. 1. *Korelacja między HbA_{1c} i wskaźnikiem Gensiniego u pacjentów z cukrzycą i przedwczesną CAD*

Table 3. Linear multivariate regression analysis for Gensini score
Tabela 3. *Wieloczynnikowa regresja liniowa dla wskaźnika Gensiniego*

		Unstandardized coefficients		Standardized coefficients	*t*	Significance
		B	Standard error	β		
Non-diabetics	(Constant)	0.179	0.746		0.241	0.811
	Age	**0.047**	**0.020**	**0.271**	**2.372**	**0.021**
	GGT	–0.004	0.005	–0.112	–0.888	0.378
	HbA_{1c}	–0.055	0.034	–0.208	–1.612	0.112
	HT	**–0.290**	**0.119**	**–0.299**	**–2.437**	**0.018**
	Smoking	0.012	0.109	0.014	0.114	0.909
Diabetics	(Constant)	1.246	0.820		1.519	0.133
	Age	–0.021	0.022	–0.098	–0.930	0.356
	GGT	0.001	0.004	0.034	0.306	0.760
	HbA_{1c}	**0.125**	**0.036**	**0.387**	**3.499**	**0.001**
	HT	**0.232**	**0.113**	**0.235**	**2.051**	**0.044**
	Smoking	0.151	0.112	0.150	1.347	0.182

Dependent variable: Gensini score. GGT – γ-glutamyltransferase, HT – hypertension, DM – diabetes mellitus

(β = 0.387, p = 0.001 and β = 0.235, p = 0.044). Also, effects of age, GGT levels and smoking were not found on the Gensini score (Table 3).

Discussion

The importance of GGT in atherosclerosis, particularly in CAD, was reported in several previous studies; but in this study, we evaluated the relationship between GGT levels and severity of CAD using the Gensini score in premature CAD for the first time in the literature. The main findings of this study are as follows: firstly, serum GGT levels were not significantly increased in patients in premature CAD groups, compared with angiographically normal coronary arteries. Secondly, GGT levels were found not to be correlated with the severity of CAD in premature CAD groups, but HbA_{1c} levels were found to be correlated with the severity of CAD in diabetic premature CAD patients.

The main mechanism of the relationship between GGT and atherosclerosis, particularly CAD, is thought to be through oxidative stress [8]. γ-Glutamyltransferase catabolizes glutathione, an intracellular antioxidant molecule, extracellularly and glutathione decreases with increasing levels of GGT. Namely, as the catabolism of glutathione increases with increasing GGT, the oxidative stress effect on tissues may increase in line. Many studies have shown GGT to be related to oxidative stress [13, 14]. Moreover, it has been revealed that serum GGT plays an important role in the pathogenesis of atherosclerosis because of triggering the oxidation of LDL-C. Additionally, a significant role of oxidative stress in the formation and progression of coronary artery disease and acute coronary syndromes was revealed [15].

Ruttmann *et al.* reported a strong association between high GGT levels and cardiovascular mortality in a large-scale study [10]. Also, they found high GGT levels to be an independent risk factor for cardiovascular disease. In that study, GGT was evaluated as a risk factor for cardiovascular disease mortality, but unlike our study, assessment in terms of severity was not done. Also differently, we studied patients with premature CAD under the age of 40. In a similar study, Demircan *et al.* found GGT activity to be higher in CAD patients than the control group [16]. They also assessed the extent of CAD by grouping patients according to the number of major coronary arteries involved; but they could not find serum GGT activity to be different between patients with 1-, 2-, and 3-vessel CAD. Similar to that study, we did not find an association between severity of CAD and GGT.

The possible relation between GGT and CAD in many studies could not be found in our study. More precisely, the expected relationship between the severity of CAD and GGT in premature CAD patients was not found in our study. We consider that this result may be due to the attenuation of the oxidative defense mechanism in older ages. In other words, the importance of GGT becomes more apparent in older ages, when the defense mechanisms are weakened and oxidative stress is more effective. The most effective protection against free radicals is rendered by various intracellular enzymes such as superoxide dismutase, catalase and glutathione peroxidase. In older ages, the protective capability of these important enzymes starts to wane [17, 18]. So, because of the effective oxidative defense mechanisms in the young population, the relationship between the severity of CAD and GGT may not become apparent.

In a recent study, Khan *et al.* reported GGT to be a biomarker for screening of premature coronary artery disease [11]. In this study, they reported the superior diagnostic accuracy of GGT at a cutoff of 35 U/l with a sensitivity of 92% and specificity of 81%. Their study was composed of 111 coronary atherosclerotic patients, whose atherosclerotic coronary artery lesion was considered significant only if at least 70% stenosis was present in one of the main coronary arteries. Also, they studied patients under the age of 45. In contrast to that study, we did not find an association between severity of CAD and GGT. Our study population was composed of 181 premature CAD patients under the age of 40 years. And unlike our study, they did not use the Gensini score system for the severity of CAD. The Gensini score is a more accurate method in the evaluation of severity of CAD because the Gensini scoring system is a quantitative digital method that shows the severity of CAD.

Also, another finding of our study was that HbA_{1c} levels were correlated with the severity of CAD in diabetic premature CAD patients. As known, HbA_{1c} is an indicator of glycemic control over the preceding 2-3 months. It has been revealed as an independent risk factor for cardiovascular events in many studies [19-21]. The results we found about HbA_{1c} are the expected results when these data are taken into consideration. Also in another study about HbA_{1c}, on patients with transplant coronary artery disease, an association was shown between transplant CAD and HbA_{1c} [22].

We evaluated the severity of CAD by coronary angiography. It shows the vessel lumen mainly. Another method, intravascular ultrasound, could be more suitable for this purpose, as it provides more accurate evaluation of atherosclerosis in the vessel lumen and throughout the vessel wall. Unfortunately, we did not have an opportunity to use intravascular ultrasound. Another limitation of the present study is the relatively small number of subjects. Also, there were relatively few female participants in this study because CAD is less prevalent in this age group.

Conclusions

The association between CAD existence and GGT levels has been reported in many previous studies. However, a relationship between the severity of premature CAD and GGT levels has not been revealed. In this study we evaluated this relationship for the first time, but we could not find a correlation between GGT levels and premature CAD severity. Possibly, effectively functioning oxidative defense mechanisms in young ages led to this statistical insignificance, because the relationship between GGT and CAD is thought to be mainly via oxidative stress.

References

1. Reddy KS, Yusuf S. Emerging epidemic of cardiovascular disease in developing countries. Circulation 1998; 97: 596-601.
2. Berenson GS, Wattigney WA, Tracy RE, et al. Atherosclerosis of the aorta and coronary-arteries and cardiovascular risk-factors in persons aged 6 to 30 years and studied at necropsy (the Bogalusa Heart-Study). Am J Cardiol 1992; 70: 851-858.
3. Cam SF, Sekuri C, Tengiz I, et al. The G894T polymorphism on endothelial nitric oxide synthase gene is associated with premature coronary artery disease in a Turkish population. Thromb Res 2005; 116: 287-292.
4. Schleicher E, Friess U. Oxidative stress, AGE, and atherosclerosis. Kidney Int Suppl 2007; S17-S26.
5. Kotani K, Shimohir H, Adach S, et al. The association between an increased level of gamma-glutamyl transferase and systolic blood pressure in diabetic subjects. Tohoku J Exp Med 2008; 214: 321-325.
6. Lee DS, Evans JC, Robins SJ, et al. Gamma glutamyl transferase and metabolic syndrome, cardiovascular disease, and mortality risk – The Framingham Heart Study. Arterioscler Throm Vas 2007; 27: 127-133.
7. Onat A, Can G, Ornek E, et al. Serum gamma-glutamyltransferase: independent predictor of risk of diabetes, hypertension, metabolic syndrome, and coronary disease. Obesity (Silver Spring) 2011.
8. Emdin M, Pompella A, Paolicchi A. Gamma-glutamyltransferase, atherosclerosis, and cardiovascular disease – triggering oxidative stress within the plaque. Circulation 2005; 112: 2078-2080.
9. Peer A, Falkensammer G, Alber H, et al. Limited utilities of N-terminal pro B-type natriuretic peptide and other newer risk markers compared with traditional risk factors for prediction of significant angiographic lesions in stable coronary artery disease. Heart 2009; 95: 297-303.
10. Ruttmann E, Brant LJ, Concin H, et al. Gamma-glutamyltransferase as a risk factor for cardiovascular disease mortality: an epidemiological investigation in a cohort of 163,944 Austrian adults. Circulation 2005; 112: 2130-2137.
11. Khan DA, Shabbir S, Khan FA. Serum gamma glutamyltransferase: a novel biomarker for screening of premature coronary artery disease. Clin Chem 2009; 55: A51.
12. Gensini GG. A more meaningful scoring system for determining the severity of coronary heart-disease. Am J Cardiol 1983; 51: 606-607.
13. Dominici S, Paolicchi A, Lorenzini E, et al. gamma-Glutamyltransferase-dependent prooxidant reactions: a factor in multiple processes (Reprinted from Thiol Metabolism and Redox Regulation of Cellular Functions). Biofactors 2003; 17: 187-198.
14. Postorino M, Marino C, Tripepi G, et al. Gammaglutamyltransferase in ESRD as a predictor of all-cause and cardiovascular mortality: another facet of oxidative stress burden. Kidney Int 2008; 74: S64-S66.
15. Libby P, Theroux P. Pathophysiology of coronary artery disease. Circulation 2005; 111: 3481-3488.
16. Demircan S, Yazici M, Durna K, et al. The importance of gamma-glutamyltransferase activity in patients with coronary artery disease. Clin Cardiol 2009; 32: 220-225.
17. Oliveira BF, Nogueira-Machado JA, Chaves MM. The role of oxidative stress in the aging process. Sci World J 2010; 10: 1121-8.
18. Romano AD, Serviddio G, de Matthaeis A, et al. Oxidative stress and aging. J Nephrology 2010; 23 Suppl 15: S29-S36.
19. Eeg-Olofsson K, Cederholm J, Nilsson PM, et al. New aspects of HbA1c as a risk factor for cardiovascular diseases in type 2 diabetes: an observational study from the Swedish National Diabetes Register (NDR). J Intern Med 2010; 268: 471-482.

20. Liu Y, Yang YM, Zhu J, et al. Prognostic significance of hemoglobin A1c level in patients hospitalized with coronary artery disease. A systematic review and meta-analysis. Cardiovasc Diabetol 2011; 10: 98.
21. Selvin E, Steffes MW, Zhu H, et al. Glycated hemoglobin, diabetes, and cardiovascular risk in nondiabetic adults. N Engl J Med 2010; 362: 800-811.
22. Kato T, Chan MC, Gao SZ, et al. Glucose intolerance, as reflected by hemoglobin A1c level, is associated with the incidence and severity of transplant coronary artery disease. J Am Coll Cardiol 2004; 43: 1034-1041.