Scandinavian Journal of Clinical and Laboratory Investigation

ISSN: 0036-5513 (Print) 1502-7686 (Online) Journal homepage: www.tandfonline.com/journals/iclb20

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To cite this article: Hakan Uçar, Mustafa Gür, Mehmet Yavuz Gözükara, Gülhan Yüksel Kalkan, Ahmet Oytun Baykan, Caner Türkoğlu, Onur Kaypakl, Taner Şeker, Ömer Şen, Şahbettın Selek & Murat Çayl (2015) Gamma glutamyl transferase activity is Independently associated with oxidative stress rather than SYNTAX score, Scandinavian Journal of Clinical and Laboratory Investigation, 75:1, 7-12, DOI: 10.3109/00365513.2014.954141

To link to this article: https://doi.org/10.3109/00365513.2014.954141

Published online: 02 Sep 2014.

Scandinavian Journal of Clinical & Laboratory Investigation, 2015; 75: 7–12

informa
healthcare

ORIGINAL ARTICLE

Gamma glutamyl transferase activity is Independently associated with oxidative stress rather than SYNTAX score

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Abstract

Background. Gamma glutamyl transferase (GGT) is involved in the pathophysiologic process of coronary atherosclerosis. GGT activity plays a role in the catabolism of glutathione which is known as one of the major antioxidants. However, there is a lack of research on direct examination of relevance between serum GGT activity with systemic oxidative stress. ***Objectives.*** We aimed to investigate the relationship between GGT activity with systemic oxidative stress markers and the extent and complexity of coronary artery disease (CAD) assessed with SYNTAX score in stable CAD. ***Methods.*** Measurements were obtained from 359 patients with stable CAD (Mean age = 57.7 ± 10.1 years). The patients were divided into two groups according to the median GGT level (GGT < median group < 22 and GGT > median group ≥ 22). Angiography was performed and SYNTAX score was calculated in all patients. Oxidative stress markers (total oxidant status [TOS], total antioxidant capacity [TAC] and oxidative stress index [OSI]) were measured in all patients. ***Results.*** While SYNTAX score and oxidative stress markers such as TOS and OSI have been increased, TAC was decreased in GGT > median group compared with GGT < median group ($p < 0.05$, for all). GGT activity was independently associated with diabetes ($\beta = 0.106$, $p = 0.015$) and OSI ($\beta = 0.556$, $p < 0.001$) in multiple linear regression analysis. However, the independent association between GGT activity and SYNTAX score was not found in present study ($\beta = 0.063$, $p = 0.238$). ***Conclusion.*** In stable CAD, increased GGT activity within the normal range is associated with increased oxidative stress rather than increased extent and complexity of CAD.

Key Words: *Oxidative stress, GGT, SYNTAX, coronary artery disease, stable patients*

Introduction

Gamma-glutamyl transferase (GGT) enzyme is found on the surface of various cells including cardiovascular system. Serum GGT activity was found to be associated with cardiovascular diseases such as coronary artery disease (CAD) [1], stroke [2] and carotid artery disease [3], cardiovascular risk factors such as diabetes [4] and hypertension [5], and prognosis of acute coronary syndrome [6,7]. GGT has also been identified in atherosclerotic plaques including coronary arteries [8,9].

At physiologic serum levels, GGT acts as a protein catalyst in the degradation of glutathione which is known as one of the major antioxidants [10]. This catabolic process leads to oxidative events such as increased production of reactive oxygen species and low density lipoprotein (LDL) oxidation which are known to be major factors playing a central role in the pathogenesis of atherosclerosis [11].

Most of studies have recommended that GGT can be used as a marker of the oxidative status [10,12]. However, there is a lack of research on direct examination of relevance between serum GGT activity with systemic oxidative stress in patients with stable CAD. We aimed to investigate the relationship between GGT activity with systemic oxidative stress markers such as total oxidant status (TOS), total antioxidant capacity (TAC), oxidative stress index

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(Received 2 February 2014; accepted 9 August 2014)

ISSN 0036-5513 print/ISSN 1502-7686 online
DOI: 10.3109/00365513.2014.954141

(OSI) and the extent and complexity of CAD assessed with SYNTAX score in stable CAD.

Methods

Study populations

In all, 359 consecutive patients (181 males and 178 females; mean age: 57.7 ± 10.1 years) with angiographically proven CAD were admitted to our cardiology clinic for angiography between January 2013 and June 2013 were included in the study. The patients admitted for elective coronary angiography were invited to participate. Angiography was performed for the investigation of ischemic heart disease based on clinical indications (typical chest discomfort and/or abnormal stress test results such as positive treadmill test, dobutamine stress echo and myocardial perfusion scintigraphy). The patients with coronary lesions with a diameter stenosis $\geq 50\%$, in vessels ≥ 1.5 mm were included the study. All patients were clinically stable.

Exclusion criteria were based on the presence of neoplastic disease, heart failure, recent major surgical procedure, kidney disease. At the same time, we excluded patients with increased hepatic markers (alanine transaminase/aspartate transaminase), history of chronic alcohol intake, hepatic steatosis and hepatic failure. Patients with previous myocardial infarction and angina episodes 48 hours before hospitalization who had undergone coronary angioplasty or bypass surgery and those with valvular, myocardial, or pericardial disease were also excluded. The patients using antioxidant vitamins such as E and C were also excluded from the study. The study was conducted according to the recommendations set forth by the Declaration of Helsinki on Biomedical Research Involving Human Subjects. The Institutional Ethics Committee approved the study protoco and each participant provided written informed consent.

Participants details were documented including medical history, physical examination and cardiovascular risk factors such as age, sex, diabetes mellitus, smoking status, and hypertension. In addition, body mass index (BMI) and systolic blood pressure (SBP) and diastolic blood pressure (DBP) were recorded.

Transthoracic echocardiography was performed in all study subjects by using a commercially available system (Vivid 7®, GE Medical Systems, Horten, Norway). Left ventricular ejection fraction (EF) was determined by modified Simpson's method [13].

Blood samples

Blood samples were immediatedly refrigerated after being collected in heparinized tubes the day before coronary angiography and after an overnight fast in all subjects. Plasma was separated from cells by centrifugation at 3000 rpm for 10 min. Plasma samples were stored at -80°C until analysis.

Plasma fasting glucose, triglyceride, LDL, high density lipoprotein (HDL) and total cholesterol levels were measured by automated chemistry analyzer (Abbott, Aeroset, MN, USA) by using commercial kits (Abbott, USA). High-sensitivity C reactive protein (hs-CRP) was measured using a BN2 model nephelometer (Siemens, Japan).

Plasma GGT activities were measured by the enzymatic calorimetric test (Roche/Hitachi analyzer, Mannheim, Germany) and the normal range of GGT activity was recognized as 7–49 U/L. The patients were classified to two groups according to their GGT activities (GGT $<$ median group $<$ 22 U/L and GGT $>$ median group ≥ 22 U/L).

Measurement of oxidative stress markers

The total antioxidant capacity (TAC) and total oxidant status (TOS) levels of serum were measured as described previously [14,15]. The oxidative stress index (OSI) was calculated as the ratio of TOS to TAC.

The unit for total antioxidative capacity of plasma, is expressed as mmol Trolox equivalent/L, and the total oxidant status of plasma as the micromolar hydrogen peroxide equivalent per liter (μmol H2O2 Eq/L). OSI is calculated as the percentage ratio of the total peroxide to the TAS level [16].

Coronary angiography and SYNTAX score

All patients underwent coronary angiography with the Judkins technique. Coronary angiography was performed with standard femoral approach with a 6-F diagnostic catheter. Coronary lesions leading to $\geq 50\%$ diameter stenosis in ≥ 1.5 mm vessels were scored separately and added together to provide the cumulative SYNTAX score which was prospectively calculated using the SYNTAX score algorithm on the baseline diagnostic angiogram [17]. Two experienced interventional cardiologists analyzed the SYNTAX score; the opinion of a third analyst was obtained and the final judgment was made by unamimous consensus. The final score was calculated from the individual lesion scores by analysts who were blinded to procedural data and clinical outcome.

Statistical analysis

All analyses were conducted using SPSS 17.0 (SPSS for Windows 17.0, Chicago, IL, USA). Continuous variables were expressed as mean + standard deviation (SD) and categorical variables were expressed as percentages. Comparison of categorical variables between the groups was performed using the Chi-square test. Analysis of normality was performed with the Kolmogorov-Smirnov test. Comparisons of continuous variables between the two groups were performed using the independent samples *t*-test. The correlation between GGT and oxidative stress mark-

ers, angiographic, clinical and laboratory parameters was assessed by the Pearson correlation test. Multiple linear regression analysis was performed to identify the independent relations of GGT by including the parameters which were correlated with GGT on bivariate analysis.

Results

Comparison of baseline characteristics (Table I)

GGT > median group have higher age, SBP and triglyceride values compared with GGT < median group ($p < 0.05$, for all). On the other hand, HDL level of GGT > median group was lower than GGT < median group ($p < 0.05$). Diabetes, hypertension, oral anti-diabetic drug use and male gender frequencies of GGT > median group were higher than GGT < median group ($p < 0.05$). SYNTAX score was higher in GGT > median group compared with GGT < median group ($p < 0.05$).

Comparison of oxidative stress markers (Table II)

TOS and OSI levels were higher in GGT > median group compared with GGT < median group ($p < 0.05$, for all). On the other hand, TAC value of GGT > median group was lower than GGT < median group ($p < 0.05$).

Bivariate and multivariate relationships of GGT (Table III)

Gamma Glutamyl transferase activity was correlated with age ($r = 0.128$, $p = 0.015$), SYNTAX score ($r = 0.414$, $p < 0.001$), OSI ($r = 0.622$, $p < 0.001$), TOS ($r = 0.653$, $p < 0.001$), TAC ($r = -0.421$,

Table I. Comparison of baseline, clinical, laboratory, echocardiographic and angiographic characteristics of groups.

Variables	GGT < median group ($n = 179$)	GGT > median group ($n = 180$)	p value
Baseline characteristics			
Age (years)	56.2 ± 10.5	59.1 ± 9.6	0.007
Gender (male)*	80 (44.9%)	100 (55.2%)	0.032
BMI (kg/m^2)	29.2 ± 7.4	29.7 ± 5.4	0.500
SBP (mmHg)	121.5 ± 18.6	131.3 ± 18.6	<0.001
DBP (mmHg)	82.7 ± 13.9	83.5 ± 11.9	0.869
Heart rate (beat/min)	77.5 ± 12.4	78.7 ± 14.4	0.389
Risk factors			
Smoking, *n* (%)*	57 (31.8%)	67 (37.2%)	0.168
Diabetes, *n* (%)*	35 (19.6%)	67 (37.2%)	<0.001
Hypertension, *n* (%)*	57 (36.3%)	83 (42.2%)	0.004
Family history, *n* (%)*	48 (26.7%)	40 (22.3%)	0.204
Hyperlipidemia, *n* (%)*	28 (15.6%)	25 (13.9%)	0.375
Laboratory findings			
Total cholesterol (mmol/L)	11.1 ± 2.44	11.4 ± 2.22	0.312
Triglyceride (mmol/L)	8.26 ± 3.99	10.4 ± 8.1	0.001
HDL (mmol/L)	2.57 ± 1.07	2.33 ± 0.61	0.024
LDL (mmol/L)	6.88 ± 1.99	6.99 ± 1.77	0.641
Fasting glucose (mmol/L)	6.71 ± 3.3	6.54 ± 2.77	0.591
Creatinin (umol/L)	68.6 ± 18.6	70.7 ± 16.7	0.171
Hemoglobin(mmol/L)	0.72 ± 0.05	0.72 ± 0.07	0.952
Hs-CRP (mg/L)	0.44 ± 0.57	0.51 ± 0.56	0.283
Echocardiographic findings			
Ejection fraction, %	64.8 ± 5.7	65.5 ± 6.0	0.242
LA diameter, mm	3.5 ± 0.4	3.5 ± 0.5	0.627
LVID, mm	4.5 ± 0.6	4.5 ± 0.6	0.872
Angiographic findings			
SYNTAX score	10.4 ± 7.6	14.4 ± 8.1	<0.001
Previous medications			
Statin use, *n* (%)*	20 (11.2%)	21 (11.7%)	0.508
OAD use, *n* (%)*	35 (19.6%)	61 (33.9%)	0.002
Beta blocker use, *n* (%)*	23 (12.8%)	18 (10.0%)	0.248
ACE inhibitor use, *n* (%)*	16 (8.9%)	14 (7.8%)	0.418
ARB use, *n* (%)*	21 (11.7%)	17 (9.4%)	0.297
ASA use, *n* (%)*	15 (8.4%)	14 (7.8%)	0.494

*Chi-square. Abbreviations: GGT, gamma glutamyl transferase; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high density lipoprotein; LDL, low density lipoprotein; Hs-CRP, high sensitive C reactive protein; LA, left atrium; LVID, left ventricle internal diameter; OAD, oral anti-diabetic; ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; ASA, acetyl salicylic acid.

Table II. Comparison of oxidative stress markers between the groups.

Variables	GGT < median group (179)	GGT > median group (180)	*p* value
TOS (μmol H_2O_2 Eq/L)	8.2 ± 1.3	10.2 ± 2.1	<0.001
TAC (μmol trolox Eq/L)	1.16 ± 0.17	1.02 ± 0.18	<0.001
OSI (arbitrary unit)	7.4 ± 2.1	10.5 ± 3.6	<0.001

TOS; total oxidant status, TAC; total antioxidant capacity, OSI; oxidative stress index

$p < 0.001$), diabetes ($r = 0.322$, $p < 0.001$), hypertension ($r = 0.238$, $p < 0.001$), SBP ($r = 0.224$, $p < 0.001$), triglyceride level ($r = 0.175$, $p = 0.001$) and HDL cholesterol level ($r = -0.147$, $p = 0.006$) in bivariate analysis. Relationships between GGT activity with OSI and SYNTAX score are shown in Figures 1 and 2.

Multivariate linear regression analysis showed that GGT activity was independently associated with OSI ($\beta = 0.556$, $p < 0.001$) and diabetes ($\beta = 0.106$, $p = 0.015$).

Multivariate relationships of SYNTAX score (Table IV)

SYNTAX score was independently associated with age ($\beta = 0.147$, $p = 0.007$), OSI ($\beta = 0.569$, $p < 0.001$) and diabetes ($\beta = 0.191$, $p = 0.001$) in multiple linear regression analysis.

Discussion

Our study results indicate that baseline serum GGT activity was independently associated with the systemic oxidative stress as well as diabetes in stable CAD. The present study showed that GGT activity was related with SYNTAX score in bivariate analysis, but this relationship was not observed in multiple linear regression analysis.

Table III. Bivariate and multivariate relationships of gamma glutamyl transferase activity.

Variables	Pearson correlation coefficient	*p* value	Standardized β-regression coefficients	*p* value
Age	0.128	0.015	−0.083	0.127
SYNTAX score	0.414	<0.001	0.063	0.187
OSI	0.622	<0.001	0.556	<0.001
TOS	0.653	<0.001	–	–
TAC	−0.421	<0.001	–	–
Diabetes	0.322	<0.001	0.106	0.015
Hypertension	0.238	<0.001	0.074	0.106
SBP	0.224	<0.001	–	–
Triglyceride	0.175	0.001	0.055	0.204
HDL-C	−0.147	0.006	−0.051	0.235

SBP, systolic blood pressure; HDL, high density lipoprotein; TOS, total oxidant status; TAC, total antioxidant capacity; OSI, oxidative stress index

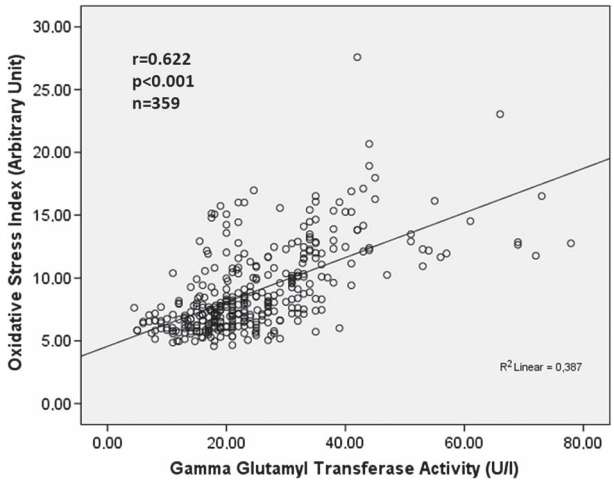

Figure 1. Relationship between gamma glutamyl transferase activity and oxidative stress index.

Relationship between GGT activity and CAD was reported in several studies [1,6–9,18]. GGT has been demonstrated in atherosclerotic plaques including carotid, cerebral, coronary artery and histochemical evidence of GGT activity was detected in human atherosclerotic plaques [2,8,19]. Moreover, previous studies have reported that serum GGT activities have predictive value for cardiovascular disease and mortality in the general population [20,21]. In addition, GGT activity has been showed to be an independent risk factor for myocardial infarction and cardiac mortality in patients with CAD [6,7,22]. In patients with ST elevation myocardial infarction undergoing primary percutaneous intervention, high GGT levels at admission were found to be associated with no-reflow phenomenon and increased long-term mortality [22]. Dogan et al. reported that increased GGT activity can be associated with significant stenosis and major cardiac events in acute coronary syndrome patients [18].

Several mechanisms have been implicated as underlying the association of GGT and cardiovascu-

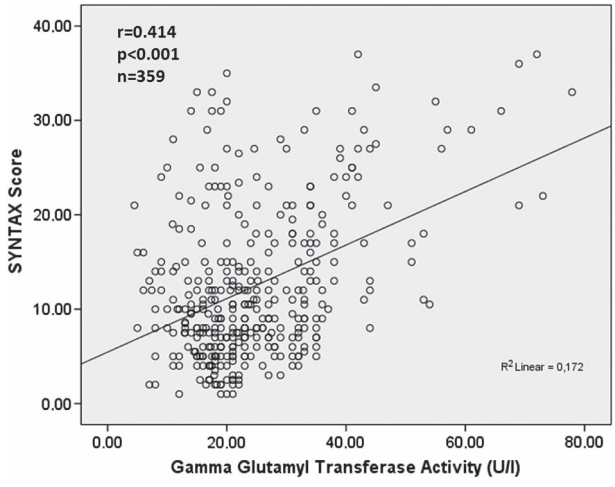

Figure 2. Relationship between gamma glutamyl transferase activity and SYNTAX score.

Table IV. Bivariate and multivariate relationships of SYNTAX score.

Variables	Pearson correlation coefficient	*p* value	Standardized β-regression coefficients	*p* value
Age	0.246	<0.001	0.147	0.007
Diabetes	0.292	<0.001	0.191	0.001
TOS	0.535	<0.001	–	
TAC	−0.455	<0.001	–	
OSI	0.623	<0.001	0.569	<0.001
SBP	0.129	0.015	−0.016	0.720
GGT	0.414	<0.001	0.037	0.497

TOS, total oxidant status; TAC, total antioxidant capacity; OSI, oxidative stress index; SBP, systolic blood pressure; GGT, gamma glutamyl transferase.

lar disease. There is growing evidence that increased oxidative stress has been regarded as one of the most important contributors to the progression of atherosclerosis [23]. Oxidative stress alters normal endothelial function supporting proinflammatory, prothrombotic, proliferative and vasoconstrictor mechanisms that support the atherogenic process [12,24]. Previous studies suggested that oxidative stress both localized and systemic plaques may link GGT with cardiovascular disease [25]. Also, several studies demonstrated that an elevated serum GGT activity can be used as a marker for increased oxidative stress in humans [12,26]. The present study shows that GGT activity is independently associated with increased oxidative stress. However, in previous studies, the relationship between GGT activity with systemic oxidative stress markers was not studied in CAD. GGT is an enzyme responsible for the extracellular catabolism of glutathione and has a role in oxidation of LDL cholesterol in atherosclerotic plaque and progression of atherosclerosis [10,11]. On the other hand, ectoplasmic GGT has been implicated in the generation of reactive oxygen species and consistent evidence supports its role as a marker of systemic oxidative stress [26]. Therefore, in the present study, the relationship between systemic oxidative stress and GGT activity was believed plausible.

Previous studies showed that GGT activity was found to be related with severity of CAD [1,18]. On the other hand, Demircan et al. showed that increased GGT activity was related to left ventricular function, clinical stability and inflammatory activity rather than the severity of CAD. However, in the above-mentioned studies, oxidative stress markers were not investigated as detailed. In the present study, GGT activity was associated with the extent and complexity of CAD assessed with SYNTAX score in bivariate analysis. However, this relationship was not observed in multiple linear regression analysis. In the present study, the strong association between GGT activity and oxidative stress index may be the suppressed association between GGT activity and SYNTAX score in multivariate analysis. Furthermore, the present study showed that SYNTAX score was independently associated with OSI as well as age and diabetes. This result is consistent with previous studies [12,23,24,27–29]. In previous studies, it was showed that antioxidant paraoxonase activity was independently associated with severity of CAD [27,28]. Stevuljevic et al. reported that the relationship between oxidative stress parameters and inflammatory species suggest their strong mutual involvement in atherosclerosis development that leads to CAD progression. [29].

In the present study, GGT activity was also related with diabetes in multiple linear regression analysis. The relationship between GGT activity and diabetes was reported in previous studies [4,30,31]. In the CARDIA study, serum GGT activity within a range regarded as normal was associated with incident diabetes mellitus and hypertension [30]. Recently, it was showed that GGT activity was strongly associated with diabetes risk in ARIC study [31]. KERCADRS study reported that measuring GGT was a sensitive method for early diagnosis and predicting impaired glucose tolerance and metabolic syndrome from normal condition [32]. Therefore, in the present study, an independent association between GGT activity and diabetes may be conceivable.

Study limitations

Serum GGT activity has been investigated in present study. However, in the present study, GGT activity has not been identified in atherosclerotic plaques. The studies investigating relationship between GGT activity in atherosclerotic plaques and systemic oxidative stress may valuable in the future studies. Medications taken before entry into the study were continued in our study. In the present study, past medications such as statin use may affect oxidative stress [33]. However, previous medications except oral antidiabetic drug use did not differ between the groups. Also, in our study, GGT activity was not independently associated with previous medications.

In conclusion, increased GGT activity within the normal range depends on increased oxidative stress rather than increased extent and complexity of CAD in stable CAD.

Declaration of interest: The authors report no conflict of interest. The authors alone are responsible for the content and writing of the paper.

References

[1] Aksakal E, Tanboga IH, Kurt M, Kaygın MA, Kaya A, Isik T, Ekinci M, Sevimli S, Acikel M. The relation of serum gamma-glutamyl transferase levels with coronary lesion complexity and long-term outcome in patients with stable coronary artery disease. Atherosclerosis 2012;221:596–601.

[2] Emdin M, Passino C, Donato L, Paolicchi A, Pompella A. Serum gamma-glutamyltransferase as a risk factor of ischemic stroke might be independent of alcohol consumption. Stroke 2002;33:1163–4.

[3] Cho SH, Jeong MH, Park IH, Choi JS, Yoon HJ, Kim KH, Hong YJ, Park HW, Kim JH, Ahn Y, Cho JG, Park JC, Kang JC. Endothelial dysfunction, increased carotid artery intima-media thickness and pulse wave velocity, and increased level of inflammatory markers are associated with variant angina. J Cardiol 2009;54:183–91.

[4] Onat A, Can G, Örnek E, Çiçek G, Ayhan E, Do anY. Serum γ-glutamyltransferase: independent predictor of risk of diabetes, hypertension, metabolic syndrome, and coronary disease. Obesity (Silver Spring) 2012;20:842–8.

[5] Kim NH, Huh JK, Kim BJ, Kim MW, Kim BS, Kang JH. Serum gamma-glutamyl transferase level is an independent predictor of incident hypertension in Korean adults. Clin Exp Hypertens 2012;34:402–9.

[6] Emdin M, Passino C, Michelassi C, Titta F, L'abbate A, Donato L, Pompella A, Paolicchi A. Prognostic value of serum gamma-glutamyl transferase activity after myocardial infarction. Eur Heart J 2001;22:1802–7.

[7] Stojakovic T, Scharnagl H, Trauner M, Pieske B, Wellnitz B, Seelhorst U, Schilling D, Winkelmann BR, Boehm BO, März W. Serum gamma-glutamyl transferase and mortality in persons undergoing coronary angiography – The Ludwigshafen Risk and Cardiovascular Health Study. Atherosclerosis 2010;208:564–71.

[8] Paolicchi A, Emdin M, Ghliozeni E, Ciancia E, Passino C, Popoff G, Pompella A. Images in cardiovascular medicine. Human atherosclerotic plaques contain gamma-glutamyl transpeptidase enzyme activity. Circulation 2004:109:1440.

[9] Niccoli G, Della Bona R, Cosentino N, D'Amario D, Belloni F, Conti MG, Gustapane M, Fracassi F, Biasucci LM, Falcioni E, Antonazzo Panico R, Crea F. Serum levels of γ-glutamyltransferase and progression of coronary atherosclerosis. Coron Artery Dis 2013;24:40–7.

[10] Mason JE, Starke RD, Van Kirk JE. Gamma-glutamyl transferase: a novel cardiovascular risk biomarker. Prev Cardiol 2010;13:36–41.

[11] Whitfield JB. Gamma glutamyl transferase. Crit Rev Clin Lab Sci 2001;38:263–355.

[12] Emdin M, Pompella A, Paolicchi A. Gamma-glutamyltransferase, atherosclerosis, and cardiovascular disease: triggering oxidative stress within the plaque. Circulation 2005;112: 2078–80.

[13] Schiller NB, Shah PM, Crawford M, DeMaria A, Devereux R, Feigenbaum H, Gutgesell H, Reichek N, Sahn D, Schnittger I. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. J Am Soc Echocardiogr 1989; 2:358–67.

[14] Erel O. A novel automated method to measure total antioxidant response against potent free radical reactions. Clin Biochem 2004;37:112–9.

[15] Erel O. A new automated colorimetric method for measuring total oxidant status. Clin Biochem 2005;38:1103–11.

[16] Aslan M, Cosar N, Celik H, Aksoy N, Dulger AC, Begenik H, Soyoral YU, Kucukoglu ME, Selek S. Evaluation of oxidative status in patients with hyperthyroidism. Endocrine 2011;40:285–9.

[17] Sianos G, Morel MA, Kappetein AP, Morice MC, Colombo A, Dawkins K van den Brand M, Van Dyck N, Russell ME, Mohr FW, Serruys PW. The SYNTAX score: an angiographic tool grading the complexity of coronary artery disease. EuroIntervention 2005;1:219–27.

[18] Dogan A, Icli A, Aksoy F, Varol E, Erdogan D, Ozaydin M, Kocyigit S. Gamma-glutamyltransferase in acute coronary syndrome patients without ST elevation and its association with stenotic lesion and cardiac events. Coron Artery Dis 2012;23:39–44.

[19] Franzini M, Corti A, Martinelli B, Del Corso A, Emdin M, Parenti GF, Glauber M, Pompella A, Paolicchi A. Gamma-glutamyltransferase activity in human atherosclerotic plaques – biochemical similarities with the circulating enzyme. Atherosclerosis 2009;202:119–27.

[20] Ruttmann E, Brant LJ, Concin H, Diem G, Rapp K, Ulmer H; Vorarlberg Health Monitoring and Promotion Program Study Group. Gamma glutamyltransferase as a risk factor for cardiovascular disease mortality: an epidemiological investigation in a cohort of 163,944 Austrian adults. Circulation 2005;112:2130–7.

[21] Lee DH, Silventoinen K, Hu G, Jacobs DR, Jousilahti P, Sundvall J, Tuomilehto J. Serum gamma-glutamyltransferase predicts non-fatal myocardial infarction and fatal coronary heart disease among 28,838 middle aged men and women. Eur Heart J 2006;27:2170–6.

[22] Ozcan F, Karakas MF, Ozlu MF, Akcay AB, Buyukkaya E, Kurt M, Erden G, Yuzgecer H, Yildirimkaya M, Hajro E, Balbay Y, Koc M, Yazici HU, Sen N. Effect of serum gamma-glutamyl transferase levels on myocardial perfusion and long-term prognosis after primary angioplasty in patients with acute ST-elevation myocardial infarction. J Investig Med 2012;60:1186–93.

[23] Halliwell B. Free radicals, antioxidants and human disease: curiosity, cause, or consequences? Lancet 1994;344:721–4.

[24] Nedeljkovic ZS, Gokce N, Loscalzo J. Mechanisms of oxidative stress and vascular dysfunction. Postgrad Med J 2003; 79:195–9.

[25] Fraser A, Harris R, Sattar N, Ebrahim S, Smith GD, Lawlor DA. Gamma-glutamyltransferase is associated with incident vascular events independently of alcohol intake: analysis of the British Women's Heart and Health Study and Meta-Analysis. Arterioscler Thromb Vasc Biol 2007;27:2729–35.

[26] Lee DH, Blomhoff R, Jacobs DR Jr. Is serum gamma glutamyltransferase a marker of oxidative stress? Free Radic Res 2004;38:535–9.

[27] Gur M, Aslan M, Yildiz A, Demirbag R, Yilmaz R, Selek S, Erel O, Ozdogru I. Paraoxonase and arylesterase activities in coronary artery disease. Eur J Clin Invest 2006;36:779–87.

[28] Akçay AB, Camsarı A, Ozcan T, Çiçek D, Akkuş N, Seyis S, Cimen B, Celebi B, Döven O, Cin G. The relationship between paraoxonase-1 activity and coronary artery disease in patients with metabolic syndrome. Turk Kardiyol Dern Ars 2011;39:371–7.

[29] Kotur-Stevuljevic J, Memon L, Stefanovic A, Spasic S, Spasojevic-Kalimanovska V, Bogavac-Stanojevic N, Kalimanovska-Ostric D, Jelić-Ivanovic Z, Zunic G. Correlation of oxidative stress parameters and inflammatory markers in coronary artery disease patients. Clin Biochem 2007;40:181–7.

[30] Lee DH, Jacobs DR Jr, Gross M, Kiefe CI, Roseman J, Lewis CE, Steffes M. Gamma-glutamyltransferase is a predictor of incident diabetes and hypertension: the Coronary Artery Risk Development in Young Adults (CARDIA) Study. Clin Chem 2003;49:1358–66.

[31] Schneider AL, Lazo M, Ndumele CE, Pankow JS, Coresh J, Clark JM, Selvin E. Liver enzymes, race, gender and diabetes risk: the Atherosclerosis Risk in Communities (ARIC) Study. Diabet Med 2013;30:926–33.

[32] Yousefzadeh G, Shokoohi M, Yeganeh M, Najafipour H. Role of gamma-glutamyl transferase (GGT) in diagnosis of impaired glucose tolerance and metabolic syndrome: a prospective cohort research from the Kerman Coronary Artery Disease Risk Study (KERCADRS). Diabetes Metab Syndr 2012;6:190–4.

[33] Sathyapalan T, Shepherd J, Atkin SL, Kilpatrick ES. Effect of atorvastatin and simvastatin on vitamin D, oxidative stress and inflammatory marker concentrations in patients with type 2 diabetes: a crossover study. Diabetes Obes Metab 2013;15:767–9.