

Gamma glutamyltransferase levels and its association with high sensitive C-reactive protein in patients with acute coronary syndromes

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Abstract

Background: Elevated Gamma-glutamyltransferase (GGT) level is independently correlated with conditions associated with increased atherosclerosis, such as obesity, elevated serum cholesterol, high blood pressure and myocardial infarction. It is also demonstrated that serum gamma-glutamyltransferase activity is an independent risk factor for myocardial infarction and cardiac death in patients with coronary artery disease. Although the relationship between gamma-glutamyltransferase and coronary artery disease has been reported, not many studies have shown the relationship between changes of gamma-glutamyltransferase in acute coronary syndromes and a well established coronary risk factor high sensitive C-reactive protein. (hs-CRP). **Aims:** In this study, how gamma-glutamyltransferase levels changed in acute coronary syndromes and its relationship with high sensitive C-reactive protein if any were studied. **Patients & Methods:** This trial was carried out at Kosuyolu Cardiovascular Training and Research Hospital and Van Yuksek Ihtisas Hospital, Turkey. 219 patients (177 males and 42 females) presenting with acute coronary syndrome, and 51 control subjects between September 2007 and September 2008 were included in the study. Serum gamma-glutamyltransferase, high sensitive C-reactive protein, serum lipoprotein levels and troponin I were determined. **Results:** Serum gamma-glutamyltransferase and high sensitive C-reactive protein levels were higher in acute coronary syndrome patients compared to control. There was also correlation between gamma-glutamyltransferase and high sensitive C-reactive protein levels. **Conclusion:** Serum gamma-glutamyltransferase and high sensitive C-reactive protein levels were higher in acute coronary syndrome patients. In subgroup analyses, the higher difference with Non-ST elevation myocardial infarction and ST elevation myocardial infarction groups than unstable angina oectoris group proposes a relationship between gamma-glutamyltransferase and severity of acute coronary syndromes.

Keywords: Gamma-glutamyltransferase, high sensitive C-reactive protein, acute coronary syndrome.

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Introduction

Gamma-glutamyltransferase (GGT) is the enzyme activity responsible for the extracellular catabolism of glutathione, the main thiol antioxidant in mammalian cells [1]. GGT is present on the outer surface of plasma membrane of most

cell types and in blood, where it has been shown to form complexes with several plasma components, in particular with albumin and lipoproteins [2, 3]. The determination of serum GGT activity is a well-established diagnostic test for hepatobiliary disease, and is used as a sensitive marker of

alcohol consumption and abuse [4]. In this perspective, several population studies have identified a predictive value of serum GGT for both all-cause and cardiovascular mortality. This positive correlation between GGT levels and cardiac mortality was found to be independent from alcohol consumption [5, 6, 7, 8]. Cardiovascular morbidity and mortality are in strict correlation with underlying atherosclerotic disease. Interestingly, elevated GGT level is independently correlated with conditions associated with increased atherosclerosis, such as obesity, elevated serum cholesterol, high blood pressure and myocardial infarction [6, 7, 9, 10]. It is demonstrated that serum GGT activity is an independent risk factor for myocardial infarction and cardiac death in patients with coronary artery disease (CAD) [11, 13, 14, 15]. As GGT activity is able to catalyze the oxidation of LDL [12], a process involved at various stages during progression of atherosclerotic lesions [12, 13], the possibility exists that circulating GGT may participate in the pathogenesis of cardiovascular atherosclerotic disease and its complications.

Although the relationship between GGT and coronary artery disease has been reported [11, 13, 14, 15], not many studies have shown the relationship between changes of GGT in acute coronary syndromes (ACS) and a well established coronary risk factor high sensitive C reactive protein (hs-CRP). In this study, how GGT levels changed in acute coronary syndromes and its relationship with hs-CRP if any were studied.

Patients and Methods

This trial was carried out at Kosuyolu Cardiovascular Training and Research Hospital and Van Yuksek Ihtisas Hospital in accordance with the principles outlined in the Declaration of Helsinki. The study protocol was approved by the local ethics committee, and all volunteers gave their written informed consent before enrollment. 219 patients (177 males and 42 females; age: 58 ± 13 years, mean \pm SD), presenting with acute coronary syndrome and 51 control subjects between September 2007 and September 2008 were included in the study. According to ACC/ AHA guidelines, ACS's were classified into 3 groups as unstable angina pectoris (UAP), non-ST segment elevation myocardial infarction (NSTEMI) and ST segment elevation myocardial infarction (STEMI). Patients with ST segment depression, negative T wave or normal ECG findings and negative troponin values were classified as UAP. Patients with similar ECG findings but positive troponin values were included in NSTEMI group. Patients with ST elevation and positive troponin values formed the STEMI group [14].

Patients with hepatic or systemic disease and history of alcohol/drug consumption were excluded. At admission, CAD patients were asked to provide information about family history of coronary artery disease, history of angina pectoris, previous myocardial infarction, alcohol consumption, hypertension (defined by blood pressure >140 mmHg for systolic and >90 mmHg for diastolic value in more than one determination or under treatment with

antihypertensive drugs), hypercholesterolaemia (defined by plasma cholesterol level of >220 mg/dl or under treatment with hypolipemic drugs), obesity (body mass index >30), diabetes mellitus (defined by either antidiabetic therapy or a fasting plasma glucose level of >140 mg/dl in more than one determination), non-cardiovascular diseases. Serum total cholesterol, HDL and LDL cholesterol fraction (HDL-C and LDL-C respectively), triglycerides, glucose, GGT, hs-CRP levels were recorded, body mass index was determined, and arterial pressure was obtained according to WHO guidelines. Troponin values higher than 0.01 ng/ml were regarded as positive. Blood samples were taken in the first day of admission and sent to laboratory to be stored at -70°C . Patients were admitted into intensive care unit and received appropriate standard care. Troponin was measured on a daily basis and the highest value was used for analysis. After completion of sample collection, GGT, hs-CRP, total cholesterol, LDL-C, HDL-C and triglyceride measurements were taken from samples. Results were summarized at the Table 1.

Table 1 Patients' characteristics and results

	UAP (76)	NSTEMI (48)	STEMI (95)	CONTROL (51)	P value
Age (years) (\pm SD)	55 ± 14	57 ± 12	60 ± 11	54 ± 14	NS
Male (n) (%)	61 (80%)	39 (81%)	77(81%)	41 (80%)	P=0.01
BMI(kg/m ²) (\pm SD)	$26.5(3.2)$	$27(3.4)$	$26.8(3.6)$	$27.4(3.5)$	NS
GGT(U/l) (\pm SD)	34 ± 20	64 ± 43	64 ± 40	23 ± 10	P=0.001
hs-CRP(\pm SD)	9.6 ± 5.8	14.4 ± 7.4	18.6 ± 7.2	5.3 ± 3.2	P=0.001
Tn I (\pm SD)	<0.01	1.56 ± 0.82	2.55 ± 1.62	<0.01	P= 0.001
TC (\pm SD)	195 ± 56	205 ± 40	197 ± 41	181 ± 31	NS
LDL-C (\pm SD)	132 ± 35	142 ± 36	136 ± 32	126 ± 21	NS
HDL-C(\pm SD)	37 ± 11	35 ± 10	38 ± 12	37 ± 12	NS
TG (\pm SD)	171 ± 93	180 ± 95	165 ± 98	140 ± 71	NS
HT (n) (%)	35	23	44	21	NS
Diabetes(n)(%)	37	26	45	23	NS

GGT: gamma-glutamyl transferase, TC: total cholesterol, hs-CRP: high sensitive CRP, TC: total cholesterol, LDL: low density lipoprotein, HDL: high density lipoprotein, TG: triglyceride.

Determination of GGT and hs-CRP

Lipemic or hemolysed samples were discarded due to possibility of false results. Serum obtained from fasting venous blood samples were centrifuged at 4000 rpm for 10 minutes and stored until analysis at -70°C . Kits were stored at $2-8^{\circ}\text{C}$, and standard and quality control materials were also kept at -70°C until analysis. Just before analysis, serum samples and reagents were brought into room temperature ($18-26^{\circ}\text{C}$). Quantitative measurement of serum gamma-glutamyltransferase was determined by a photometric method (Smac, Technicon). (Reference range 6-28 U/l). hs-CRP levels were measured with quantitative immunoturbidimetry method. Lower detection limit was 0,1 mg/l. Serum lipoprotein levels were measured with enzymatic calorimetric method using "Roche triglycerides", "Cholesterol gen 2", "HDL cholesterol plus 2nd generation", "LDL-Cholesterol plus 2nd generation" kits. Troponin I levels were measured using immunoassay methods.

Statistical analyses

Continuous variable values were expressed as % mean ± SD. Nominal variables were given as %. All data were tested for normal distribution with the Kolmogorov-Smirnov test. Whether a significant difference was present or not in terms of variables between groups was evaluated by ANOVA. Scheffe test was used for paired comparisons. Chi-square test was used to compare nominal variables. If necessary, Fischer’s exact test was applied. Correlations were evaluated by Pearson’s correlation coefficient. An adjusted value of $p < 0.05$ was considered to be statistically significant. All calculations were performed with SPSS version 12.0 (Chicago, Illinois).

Results

Serum GGT levels

GGT values were 23 ± 10 in control group, 34 ± 20 in UAP group, 64 ± 43 in NSTEMI group and 64 ± 40 in STEMI group. In variance analysis, a significant difference was present between all groups ($p < 0.001$). In paired comparisons, no significant difference was found between control and UAP groups (Control vs. UAP -11 ± 5.8 ($p = 0.3$)). A significant difference was found when control group was compared with STEMI and NSTEMI groups (control vs NSTEMI: -41 ± 6.5 , $p = 0.001$; control vs STEMI -40 ± 6 , $p = 0.001$). When UAP group was compared with NSTEMI and STEMI groups, significant difference was noted again (UAP vs NSTEMI -30 ± 6 , $p = 0.001$, UAP vs STEMI -29 ± 5 , $p = 0.001$). When NSTEMI and STEMI groups were compared, no statistical significant was found (-1.4 ± 5 , $p = 0.96$) (Table 1, Fig. 1).

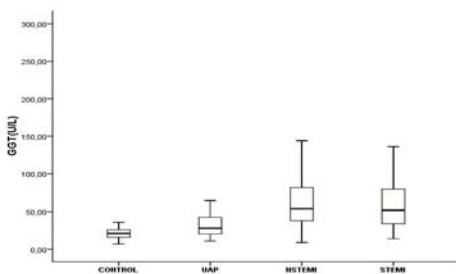


Fig. 1 GGT levels in acute coronary syndrome subgroups. There was no significant difference between control and UAP groups. A significant difference was found between control versus STEMI and control versus NSTEMI groups. When UAP group was compared with NSTEMI and STEMI groups, significant difference was noted again. There was no significant difference between NSTEMI and STEMI.

Serum hs-CRP levels

The levels of hs-CRP (Mean ±SD) were as follows: Control 5.3 ± 3.2 ; UAP 9.6 ± 5.8 ; NSTEMI 14.4 ± 7.4 ; STEMI 18.6 ± 7.2 (Table 1 and Figure 2). In variance analysis, a significant difference was present between all groups ($p < 0.001$). In paired comparisons, a significant difference was also noted between all groups ($p < 0.001$). Mean difference ±SE is as follows: Control vs. UAP -4.28 ± 1.14 ($p = 0.003$), Control vs. NSTEMI -9.10 ± 1.27 ($p < 0.001$), Control vs. STEMI -13.32 ± 1.09 ($p < 0.001$), UAP vs.

NSTEMI -4.82 ± 1.16 ($p = 0.001$), UAP vs. STEMI -9.04 ± 0.97 ($p < 0.001$), and NSTEMI vs. STEMI -4.22 ± 1.12 ($p = 0.003$).

The level of hs-CRP in control group was lower than those of the other groups. The next lowest level of hs-CRP belonged to the UAP group. hs-CRP level of NSTEMI group was significantly lower than that of STEMI group and higher than that of UAP group. The order of hs-CRP levels is Control $<$ UAP $<$ NSTEMI $<$ STEMI (Table 1 and Fig. 2).

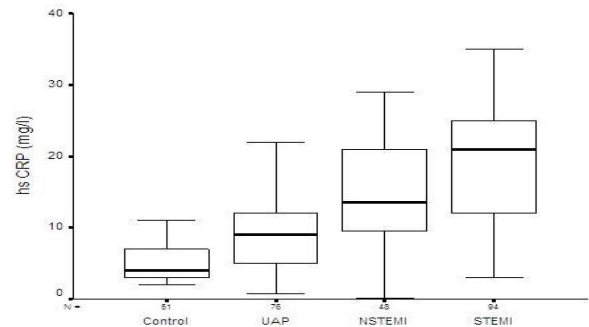


Fig. 2 hs-CRP levels (mg/l) in control and ACS subgroups. hs CRP levels were progressively increased as the disease severity worsened. The lowest hs CRP levels were in control group and the highest levels were in STEMI. Levels were higher in NSTEMI than UAP. (UAP: Unstable angina pectoris, NSTEMI: Non-ST elevation myocardial infarction, STEMI: ST elevation myocardial infarction).

Correlations

As troponin values in control and UAP groups are negative (i.e. < 0.01), statistical analyses relating troponin were done only for STEMI and NSTEMI groups. Analyses relating GGT, hs-CRP and lipid profiles were carried out for all groups. When all ACS groups were taken, a moderate but significant correlation was present between GGT and hs-CRP ($r = 0.49$ $p = 0.01$, Fig. 3). There was no correlation between GGT and lipid profiles ($r = 0.166$ $p = 0.03$ for GGT and TC, $r = 0.12$ $p = 0.04$ for GGT and LDL-C, $r = 0.18$ $p = 0.08$ for GGT and TG). The best correlation of troponin was with hs-CRP levels ($r = 0.75$ $p = 0.001$). However, troponin has no significant correlation with GGT levels ($r = 0.11$ $p = 0.08$). There was no correlation between BMI and GGT and hs CRP ($r = 0.18$ $r = 0.06$).

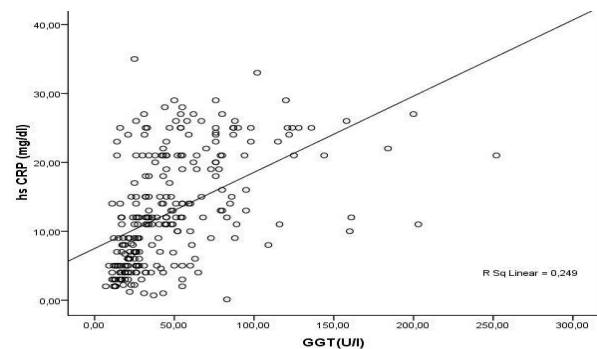


Fig 3 A moderate but significant correlation was detected between GGT and hs-CRP levels ($r = 0.49$ $p = 0.01$).

Discussion

Elevation of serum gamma-glutamyltransferase activity is a risk factor for myocardial infarction and stroke. GGT activity can catalyze the oxidation of low-density lipoprotein (LDL), a process involved in the pathogenesis of atherosclerosis [15].

There are a number of high-volume studies showing the relationship of GGT with acute coronary syndromes and cardiovascular mortality. In a prospective study, 28 838 Finnish men and women aged 25-74 years were followed up 11.9 years. Stronger association between GGT levels and fatal/non fatal events was observed among subjects aged <60 and among alcohol drinkers [16]. The relation of GGT to the risk of death from CVD was examined in another cohort of 163 944 Austrian adults that was monitored for up to 17 years. In both men and women, high GGT was significantly associated with total mortality from CVD, showing a clear dose-response relationship. In men, subgroup analyses showed that high GGT was positively associated with incident fatal events of chronic forms of coronary heart disease, congestive heart failure and hemorrhagic and ischemic stroke [17]. In a survey of 1878 men who were free of coronary heart disease at baseline followed up 18 years. Baseline levels of GGT were higher in men who experienced an event than in event-free men. GGT was highly correlated with other cardiovascular risk factors [18].

In our study, higher levels of GGT in acute coronary syndromes patients when compared to control group supports the relationship of GGT with cardiovascular mortality. In sub-group analyses, the higher difference with NSTEMI and STEMI groups than UAP group proposes a relationship between GGT and severity of acute coronary syndromes. In more severe acute coronary syndromes with higher degrees of inflammation, GGT levels are found to be consistently higher. This was also supported by the correlation between hs-CRP levels and GGT levels. Similar results were found with hs-CRP levels. However, in subgroup analyses, significant differences were also seen between UAP and control group, and NSTEMI and STEMI groups. Thus, hs-CRP proves to be a better predictor of the degree of acute coronary syndromes both clinically and anatomically. GGT, when compared to hs-CRP, seems a weaker predictor of the severity of acute coronary syndromes. As a result, GGT levels were found to be significantly higher in acute coronary syndromes than the control group. A moderate correlation was found between GGT levels and hs-CRP levels. Increase in GGT was more significant in NSTEMI and STEMI groups. No difference was found between UAP and control groups. And the difference between NSTEMI and STEMI was not significant as well.

GGT levels were measured only once at baseline, we were, therefore, unable to evaluate within-individual variability. As the GGT levels of acute coronary syndromes patients were evaluated in our study, the results could not be evaluated as in epidemiologic studies done with the

populations at risk.

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Disclose that there exist no conflict of interest and also disclose that there is no any institutional or commercial affiliations that might pose a conflict of interest regarding the publication of a manuscript. There is no other types of affiliation, including consultantships, honoraria, stock ownership, equity interests, arrangements regarding patents, or other vested interests .

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