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Original Investigation

Prognostic Value of Serum Gamma-Glutamyltransferase, Calcium, and Inorganic Phosphorus Levels in Short-Term Mortality of Patients with Acute Coronary Syndrome

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Abstract

Objective: Gamma-glutamyltransferase (GGT) may be considered as a biomarker of "oxidative stress" associated with glutathione metabolism and a possible "proatherogenic" marker because of its indirect relationship with the biochemical steps in the oxidation of low density lipoprotein cholesterol. Serum inorganic phosphorus (P) level is also suggested as an independent risk factor for cardiac events and mortality in the long term. We aimed to observe the relationship of serum GGT, calcium (Ca), and P levels with 1 months' mortality after myocardial infarction.

Methods: Our retrospective study included 200 patients (124 men and 76 women) with acute coronary syndrome (ACS) who were admitted to our hospital. We excluded subjects with severe systemic illness, hepatobiliary disease, alcohol consumption, chronic metabolic bone disease, malignancy, parathyroid disease, and patients who had a glomerular filtration rate (GFR) <60 mL/min. Fasting blood samples were taken in the first 24 h of admission to the coronary care unit (CCU). Reference values for GGT (9-36 U/L, for women; 12-64 U/L, for men), Ca (8.4-10.2 mg/dL), and inorganic P (≤4.5 mg/dL) were used. When the serum albumin level was <4.0 g/dL, corrected Ca levels were calculated using the equation [corrected Ca=measured Ca+(0.8×(4-serum albumin)]. Statistical analysis was performed using SPSS for Windows 10.0. Descriptive statistical analysis, Student's t-test, Mann-Whitney U-test, and chi-square test were used.

Results: At the end of 1 month, we found significantly higher levels of blood GGT, P, and Ca×P products in patients who did not survive (n=23; 32.9 U/L, 3.66 mg/dL, 35.93 mg^2/dL^2) than in survivors (n=177; 24.16 U/L, 3.27 mg/dL, 31.57 mg^2/dL^2; p<0.001, p<0.001, p<0.001, respectively).

Conclusion: Serum GGT, P, and Ca×P levels, even in the reference intervals, had a prognostic value in the short-term mortality apart from traditional risk factors such as diabetes mellitus, hypertension, and ischemic heart disease. This study also suggests constituting new reference values for this high risk population in stratifying patient risk and in assessing the intensity of appropriate treatment, with hopes of preventing cardiac deaths.

Keywords: Acute coronary syndrome, mortality, Gamma-glutamyltransferase, calcium, phosphorus

Introduction

Acute coronary syndrome (ACS) is one of the most common causes of morbidity and mortality in adults. In addition to conventional risk factors such as age, diabetes mellitus (DM), dyslipidemia, hypertension (HT), smoking, hyperhomocysteinemia, and high fibrinogen levels, new biomarkers, including asymmetric dimethyl arginine (ADMA), highly sensitive CRP (hsCRP), carotid intima-media thickness (CIMT), and adiponectin, have received attention (1, 2). Recently, it has been suggested that serum gamma-glutamyltransferase (GGT), a sensitive parameter in hepatobiliary and alcohol-related diseases, is an independent prognostic marker for cardiac death. GGT contributes to oxidative stress pathways in several organ systems, localizes to atheromatous plaques containing oxidized low density lipoprotein (LDL), and is proinflammatory, further implicating this protein in atherogenesis. In addition to a role in LDL oxidation during the atherosclerotic process, GGT activity is associated with other atherosclerotic risk factors, including insulin resistance, metabolic syndrome, HT, and DM (3-6). Phosphorus (P) is also an important mineral with many biological and physiological properties, and it has been suggested to play a role in vascular damage. Many studies have shown that high serum P and calcium (Ca) × P levels are related to coronary calcification and cardiovascular mortality. Vascular calcification results in arterial stiffness, decreased elasticity, increased blood pressure, and left ventricular hypertrophia (7-11). High serum P levels have also been reported with increased mortality in patients with cardiovascular disease who have normal renal function (12-15). We evaluated the association between serum GGT, Ca, inorganic phosphorus (P_i) levels and short-term cardiac mortality with variables such as age, gender, DM, HT, serum high density lipoprotein (HDL) cholesterol level, history of ischemic heart disease (IHD), clinical presentation of patients with ACS, and localization of myocardial infarction (MI).

Methods

In this study, 200 patients (124 men and 76 women) who were hospitalized in the coronary care unit (CCU) with a diagnosis of ACS were included. All patients had normal serum GGT levels

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at admission to the CCU. We excluded subjects with GGT levels beyond the reference value range, patients with known severe systemic illness, alcohol consumption (based on self-report >90 g/week), malignancy, hepatobiliary and renal disease [glomerular filtration rate (GFR) <60 mL/min/1.73 m^2 using the Cockcroft-Gault formula], and incomplete or missing data that made clear patient identification impossible. In addition to demographic characteristics, DM, HT, smoking habit, and history of IHD were evaluated as risk factors for cardiovascular disease. DM was defined as measurements of fasting blood glucose levels (≥126 mg/dL) at least twice in different samples or the use of an antidiabetic drug. HT was defined as measured systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg and/or the use of antihypertensive medication. Current smoking was self-reported and was defined as having smoked cigarettes regularly within the previous year. Clinical presentations of the patients were classified according to the diagnosis of unstable angina pectoris (USAP), ST-elevated myocardial infarction (STEMI), and non-ST-elevated myocardial infarction (NSTEMI), which took into account the symptoms, cardiac enzymes, and electrocardiogram (ECG) changes.

Serum GGT levels were measured with an enzymatic colorimetric method using L-gamma-glutamyl-3-carboxy-4-nitroanilide as a substrate at 37°C with Aeroset 2.0 (Abbott Aeroset Clinical Chemistry Analyzer, Illinois, USA) in the laboratory. The GGT reference intervals were 12-64 U/L for men and 9-36 U/L for women according to the test kit specifications.

Serum Ca and P levels were measured spectrophotometrically with an Abbott Aeroset automatic analyzer (Abbott Aeroset Clinical Chemistry Analyzer, Illinois, USA). The upper limit of P was 4.5 mg/dL, and the reference values for Ca were 8.4-10.2 mg/dL. Corrected Ca values were recorded for patients with a serum albumin level <4g/dL, according to the formula.

Based on the patient records, we contacted the patients or their close relatives to learn whether the participants were still alive or not. Cardiac death was the target end-point. Follow-up was performed by telephone contact or interviews. The cause of death within 1 month after discharge from the coronary intensive care unit was noted after detailed inquiry. Death certificates and all pertinent records were reviewed, and patients who were still alive were included. Reports of left ventriculography or selective coronary angiography performed after medical therapy of 3-7 days were acquired. At least 50% narrowness in one major coronary artery segment was defined as coronary artery disease. The Local Ethical Committee of our hospital approved the study; the patients gave their informed consent.

Statistical analysis

The SPSS 10.0 (Inc., Chicago, IL, USA) program was used for statistical analysis. Descriptive methods (mean, standard deviation), Student's t-test, the Mann-Whitney U test, and the chi-square test were used for comparisons. P<0.05 was considered statistically significant.

Results

Patient characteristics are shown in Table 1. DM was more prevalent in patients who died compared with that in those who survived (p=0.011), whereas no difference was observed for HT, coronary heart disease, or history of smoking.

In Table 2, the comparison of groups is shown based on survival.

The mean age, GGT and P levels, and Ca x P values were higher in people who died. There was no significant difference in other laboratory variables according to gender or mortality.

When we compared the groups separately, the GGT levels were high only in women who died (p=0.032 vs. 0.015). Alive or dead male patients did not show a difference. Female survivors were older than male survivors (p<0.001). The GGT levels were higher in male survivors than in female survivors (p<0.001), whereas the P and Ca × P levels in female survivors were higher than in male survivors (p<0.05).

According to the subgroup analysis, age revealed an association with DM (p=0.006) and high GGT levels in the patients with HT (p=0.008).

Discussion

Serum GGT activity has been shown to increase the development of metabolic syndrome and cardiovascular diseases and mortality risk even in normal reference values (16-18). Many studies showed that higher GGT levels were related to cardiovascular events (16, 19, 20). We also found significantly higher GGT levels, even in normal reference intervals, in short-term mortality in patients with ACS (32.96 U/L vs. 24.16 U/L, respectively, p<0.001).

Young men (<60 years) whose serum GGT levels are higher than 28 U/L (for our laboratory method) require closer follow-up after discharge from the CCU, particularly if the patient is a current smoker and is diagnosed with STEMI, independent from DM, HT, and history of IHD. Thus, men <60 years have a higher risk of mortality when they are current smokers, have GGT levels higher than 28 U/L, and have been diagnosed with inferior + right ventricular MI. We also observed higher serum GGT levels in both genders with inferior + right ventricular MI and thought about the possible association between localization of myocardial damage and GGT. Inferior + right ventricular MI possibly caused right ventricular heart failure and liver congestion. Thus, patients with inferior + right ventricular MI should be followed up with repeated serum GGT measurements to examine changes over time.

In women, higher GGT levels seem to be related to older age and metabolic syndrome and/or DM. When DM, HT, history of IHD, and low HDL cholesterol levels (<45 mg/dL) coexist, women in particular require closer follow-up after discharge from the CCU.

Onat et al. (21) reported GGT as a marker of metabolic syndrome and coronary heart disease in Turkish adults, particularly in men (1556 non-diabetics) independent of waist circumference and major risk factors. A stronger association between GGT and cardiovascular disease was shown in other studies (22-24). We did not evaluate the association of GGT with body mass index (BMI) or white blood cell (WBC) count. In addition, Ruhl et al. (25) did not find a statistically significant relationship between elevated GGT and cardiovascular disease mortality. Our study supported the findings of serum GGT levels associated with cardiovascular mortality risk in young adults in the literature.

Table 1. Patient characteristics

	Negative		Positive		Total			
Mortality	**n**	**%**	**n**	**%**	**n**	**%**	**Chi- square**	**p**
Gender								
Male	112	63.3	12	52.2	124	62.0		
Female	65	36.7	11	47.8	76	38.0	1.06	0.302
DM								
(-)	130	73.4	11	47.8	141	70.5		
(+)	47	26.6	12	52.2	59	29.5	6.42	0.011
HT								
(-)	88	49.7	8	34.8	96	48.0		
(+)	89	50.3	15	65.2	104	52.0	1.81	0.177
CHD								
(-)	119	67.2	16	69.6	135	67.5		
(+)	58	32.8	7	30.4	65	32.5	0.05	0.822
Smoking								
(-)	98	55.4	14	60.9	112	56.0		
(+)	79	44.6	9	39.1	88	44.0	0.25	0.617
ACS								
USAP	43	24.3	3	13.0	46	23.0		
NSTEMI	106	59.9	14	60.9	120	60.0		
STEMI	28	15.8	6	26.1	34	17.0	2.38	0.303

ACS: acute coronary syndrome; DM: diabetes mellitus; HT: hypertension; USAP: unstable angina pectoris; NSTEMI: non-ST-elevated myocardial infarction; STEMI: ST-elevated myocardial infarction

Table 2. Comparison of patients with and without mortality

	Negative		Positive		
Mortality	**Mean**	**SD**	**Mean**	**SD**	**p**
Age	62.21	12.42	71.26	11.98	0.001
GGT	24.16	8.46	32.96	12.84	0.000
Ca	9.66	0.42	9.79	0.44	0.171
P	3.27	0.57	3.66	0.61	0.003
Total cholesterol	194.91	49.94	179.00	49.11	0.151
LDL-C	126.95	42.57	112.48	38.12	0.123
HDL-C	38.50	13.68	39.17	13.14	0.824
Triglyceride	150.14	87.19	136.96	68.11	0.487
Ca×P	31.57	5.82	35.93	6.99	0.001

Ca: calcium; GGT: Gamma-glutamyltransferase

Ulus et al. (19) investigated GGT activity in patients who were hospitalized in the CCU with ACS; in the 1-month follow-up period, serum GGT activity was significantly higher in the patients with major adverse cardiac event [30.0 (21.0-48.0) U/L)] than those without an adverse cardiac event [23.5 (17.0-33.8) U/L]. Strasak et al. (26) observed that not only GGT but also a longitudinal increase in GGT, even within the normal range, may be related to adverse cardiovascular or cerebrovascular outcomes in men ≤60 years. Onat et al. (21) suggested optimal cutoff values of GGT for the likelihood of coronary heart disease as 50 U/L for men and 35 U/L for women. Sakuta et al. (27) observed a positive relationship between serum GGT activity and total cholesterol, triglyceride, fasting plasma glucose, total homosystein levels, and systolic blood pressure. This was also found in patients when smoking, alcohol use, or BMI was taken into account. We did not find a correlation between smoking and serum GGT values. We also excluded patients with alcohol consumption. Many studies have shown an association between serum GGT activity and DM and metabolic syndrome (28-30). We also found higher GGT levels in patients with diabetes.

A significant relation was found with GGT and HT. This was similar irrespective of whether the patients used alcohol; thus, hepatic steatosis has a common pathogenetic role in the development of HT (31, 32). We also found significantly higher GGT levels in patients with HT.

We observed higher serum GGT levels associated with mortality in men and women in correlation with other studies (33-36). In the subgroup analysis of survivors or non-survivors, we did not observe a relationship with a history of DM, HT, or coronary heart disease. Total cholesterol, LDL, HDL, and triglyceride levels did not differ between patients who died or survived. GGT activity was higher in patients with NSTEMI, whereas patients with STEMI and USAP did not show a difference with respect to the enzyme.

Increased serum Ca and P_i levels were also reported to be associated with cardiovascular mortality (37). After adjustment for age and gender, plasma calcium is a predictor of cardiovascular events. High serum P levels were shown to be related with cardiovascular events and mortality in end-stage renal disease (38-42). Numerous studies also supported that serum P level is an independent risk factor for cardiovascular diseases in subjects with normal renal function (15, 42-46). Larsson et al. (43) reported high serum P and (Ca×P) levels are predictors of total and cardiovascular mortality. According to De Boer et al. (47), the relation of elevated P and cardiovascular events was independent from

other traditional risks and the dietary P amount. We did not investigate the dietary consumption of Ca and P in our patients. In addition, we did not search for an association between vitamin D and cardiovascular risk factors. Park et al. (13) showed that lower concentrations of serum P within the previously alleged normal range were associated with a lower Agatston score, suggesting less coronary artery calcification in subjects with normal renal function. The results of our study suggest that the association between serum P concentration and Ca scores has a triangular relation between Ca score, coronary events, and serum P. Therefore, a new normal range of serum P levels without harmful effects on coronary calcification should be determined based on results, including ours, in other studies. The risk of coronary calcification was significantly higher in individuals with serum P concentration >3.9 mg/dL than in those with serum P concentration <3.3 mg/dL. Even a relatively higher concentration of serum P within the normal range could be a risk factor for cardiovascular disease.

In a study, Slinin et al. (48) found a relationship between high serum Ca level and cardiovascular events; however, they could not find an association between P levels and cardiovascular events. In our study, there was no relationship between the serum Ca levels and cardiovascular mortality, and the association of mortality and serum P and Ca × P values was observed only in men. We excluded patients with estimated GFR <60 mL/dk/1.73 m^2 according to the Cockcroft-Gault formula. However, we may have included subjects who had undiagnosed renal disease with GFR >60 mL/dk/1.73 m^2. Patients who had Ca × P >55 mg^2/dL^2 were also excluded. Although we did not measure serum parathyroid hormonal levels, we do not expect to find people with secondary hyperparathyroidism in our study group.

Study Limitations

We assessed the short-term predictive role of GGT, P, Ca, and Ca × P, which are inexpensive tests and can easily be measured in ACS. The retrospective design is an evident limitation; the inability to examine the effect of oral contraceptive and statin use, caffeinated beverage consumption, BMIvalues, hepatic steatosis, and insulin resistance on GGT levels was a limitation. Patients with impaired glucose tolerance were probably classified as non-diabetic. We included patients with ACS who had GGT values within the reference range according to the test kit specifications. However, liver-related enzymes would be elevated in non-alcoholic fatty liver disease; this group of patients was not excluded in this study. Localization of MI (right ventricular + inferior MI) was important as a cause of right ventricular failure and liver congestion. In addition, we did not extend this study to cardiac markers such as troponins or brain natriuretic peptides. We could not obtain GGT measurements of the subjects before admission to CCU to evaluate intra-individual biological variation or disease effect and time-dependent variation. The current smoking rate was quite high in our study population, particularly among men. Although patients with GFR <60 mL/min/1.73 m^2 (according to the Cockroft-Gault formula) were excluded, subjects with early stage chronic renal disease with GFR >60 mL/min may have been included.

Conclusion

Our observations related to serum GGT levels in young men and short-term mortality suggested GGT is an important component of cardiovascular risk evaluation. Serum GGT levels should be routinely tested in hospitalized patients with a diagnosis of ACS to identify a subset at the highest risk of cardiac events that require specific and enhanced therapeutic effort. Constituting reliable reference values or confirmation of differences in disease state according to gender, age, BMI, alcohol consumption, and high-risk groups (e.g., diabetics) for serum GGT levels in patients with ACS is presumably possible only after large multicenter cooperative efforts are undertaken.

We also observed a relationship between short-term mortality and serum P and serum Ca × P levels in our patient group apart from the traditional risk factors. In high-risk patients with a history of ACS, the serum P levels showed prognostic importance even in normal reference values such as ≥3.5 mg/dL. More studies are necessary to determine the prognostic and predictive role of these laboratory variables.

Ethics Committee Approval: Ethics committee approval was received for this study.

Informed Consent: Written informed consent was obtained from patient who participated in this study.

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