Gamma Glutamyl Transferase Levels in Patients with Acute Coronary Syndrome: A Cross-Sectional Study

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ABSTRACT

Background & Objectives: Oxidative stress is thought to play a key role in the progression of atherosclerosis. Many studies have identified gamma glutamyltransferase (GGT) as a marker of oxidative stress and its relationship with coronary artery disease (CAD). There is limited data exploring the changes of GGT levels in acute coronary syndrome (ACS). The objective of present study was to assess the prevalence of raised GGT and its correlates in ACS patients. Methods: A cross-sectional study was performed in Intensive cardiac coronary unit of Medicine Department in tertiary care teaching hospital. All consecutive patients of ACS more than 18 years of age were included in this study. ACS was diagnosed on the basis of history, electrocardiogram and biochemical markers. All subjects underwent test for GGT by enzymatic calorimetric method. Magnitude of raised GGT in ACS was expressed in percentage. Unadjusted odds ratio (ORs) and multivariate logistic regression analysis were computed to assess the strength of association between independent variables and dependent variables. P value ≤0.05 was considered as significant. Results: We included 323 study subjects from November 2012 to October 2014. The magnitude of raised GGT among ACS was 41.80%. The magnitude of raised GGT in non ST elevated myocardial infarction (NSTEMI), ST elevated myocardial infarction (STEMI) and unstable angina (UA) was 57.32%, 37.85% and 32.81% respectively. The significant correlate of raised GGT were male sex [OR: 3.58 (95%CI: 1.88-6.79) P=0.000] and NSTEMI as diagnosis of ACS [OR: 3.32 (95%CI: 1.51-7.30) P=0.003] in the study subjects. Interpretation and Conclusion: Gamma glutamyl transferase activity is increased in subjects with ACS. High levels of serum GGT on admission were associated with the burden of atherosclerosis in patients with ACS.

Key words: Acute coronary syndrome, Coronary artery disease, Gamma glutamyltransferase, Oxidative stress.

INTRODUCTION

Several mechanisms are known to regulate the pathogenesis of coronary artery disease and oxidative stress is one of them.1–3 Several studies demonstrated that an elevated serum GGT activity can be used as a marker for increased oxidative stress in humans.4–6 GGT is pro-inflammatory and its activity has been observed in coronary atherosclerotic plaques containing oxidized LDL.5,6 High levels of serum GGT have been shown to be associated with the development of CAD risk factors such as diabetes mellitus (DM), hypertension and metabolic syndrome.7–10 The marked relation between GGT and atherosclerotic process has shifted attention to the principal issue of whether its serum levels can aid in the detection of individuals at higher risk of incident cardiovascular events.11 Previous studies showed that measurement of GGT activity may be useful in predicting cardiovascular risk as GGT levels were higher in patients of coronary artery disease than in patients who had insignificant coronary artery disease or normal coronaries.12–14 Some Indian studies have reported that ACS patients had significantly higher levels of serum GGT as compared to controls and there was significant association with the established risk factors like abnormal body mass index (BMI), hypertriglyceridemia, DM and systolic and diastolic hypertension. In an observational study, increased GGT levels were associated with absence of coronary collateral vessels in patients with ACS.15 In a Turkish study, GGT levels were higher in STEMI and NSTEMI than UA group which proposes a relationship of GGT and severity of ACS. In more severe ACS with higher degrees of inflammation, GGT levels are found to be consistently higher.16 Although the relationship between GGT and CAD has been reported, there is very limited data exploring the changes of GGT in ACS from central India. Hence the present study was conducted to assess the prevalence of raised GGT and its correlates in ACS patients.

MATERIAL AND METHODS

A prospective, single centre, observational cross-sectional study was conducted during a 24 months period, between November 2012 till October 2014 in the intensive coronary unit of the Department of Medicine, in a 650-bedded teaching tertiary care teaching hospital from central India (Mahatma Gandhi Institute of Medical Sciences, Sevagram). Approximately 450,000 patient visits and about 10,000 patients are admitted to the Medicine wards every year. The study was approved by the ethics committee of Mahatma Gandhi Institute of Medical Sciences. We obtained a written informed consent from all study subjects before enrolling them in the study.

All consecutive patients of more than 18 years of age, admitted to the Medicine intensive coronary unit during study period, diagnosed to have ACS (index cases) were recruited for the study. Acute coronary syndrome including STEMI, NSTEMI and UA was diagnosed on a clinical basis involving relevant history, biochemical tests and ECG recording.

STEMI was defined as ST-elevation of ≥0.1mV in >1 limb leads or ≥0.2mV in contiguous chest leads or left bundle branch block on presentation to the hospital. Those without ST elevations were diagnosed either with UA or NSTEMI differentiated by the presence of cardiac enzymes. NSTEMI were defined as those having persistent or transient ST segment depression or T wave inversion, flat T waves, pseudo-normalization of T waves or no ECG changes at presentation with raised cardiac enzymes however those without raised cardiac enzymes were defined as UA.16

Patients with past history of myocardial infarction, coronary intervention, congestive heart failure, history of alcoholic liver disease, chronic obstructive pulmonary disease, recent alcohol intake i.e., less than 3 weeks, respiratory failure, renal failure, on anti-epileptic drugs (phe-
nytoin, carbamazepine, phenobarbital), on oral contraceptives and not provided written informed consent were excluded from the study. All study subjects included in the study underwent a relevant clinical history and physical examination. Demographic data including age and sex; BMI, information about major risk factors for coronary artery disease like DM, hypertension, alcohol consumption and smoking was sought in all cases. BMI reference value according to World health organization was defined as normal (18.5 - 24.9 kg/m²), underweight (< 18.5 kg/m²), overweight and obese (≥25kg/m²). Diabetes mellitus was defined as a fasting blood glucose level >126 mg/ dl or using anti diabetic drugs and hypertension was defined as blood pressure of 150/90 mmHg or more or taking antihypertensive medications. Subjects were considered as smokers if they reported smoking for at least 3 months in their life and who currently smoke at least on some days of a week.

Blood samples were obtained in fasting state in order to measure blood sugar, lipid levels (TG, total cholesterol, LDL, HDL, and VLDL) and GGT. All the study subjects were informed previously to remain fasting at-least 10 h before the blood samples were withdrawn. Creatine kinase – MB (CK-MB) and creatinine were performed on admission in all study subjects. Blood samples were collected in plain tubes and serum free from hemolysis was stored at 2 – 8°C. Serum GGT levels were measured at 37°C by enzymatic calorimetric test using a reagent L-gammaglutamyl-3-carboxy-4-nitroanilide by Auto-analyzer. For the study purpose serum GGT levels of > 32 IU/L in females and > 50 IU/L in males were considered raised.17

Statistical analysis: We used STATA software (Version 16, Stata Corporation, Texas, USA) to analyze the data. GGT was assessed for normal distribution. Since it was not normally distributed in our study, we used median and interquartile range to describe GGT. Magnitude of raised GGT among ACS was expressed in percentage. Unadjusted odds ratio (ORs) and multivariate logistic regression analysis along with their 95% confidence intervals (CIs) were computed to assess the strength of association between independent variables (age, sex, BMI, smoking, DM, hypertension, CK – MB, lipid profile, and diagnosis of ACS and dependent variables (raised GGT levels). \( P < 0.05 \) was considered as significant. To derive full model multi- collinearity was assessed by tolerance. Tolerance of 0.1 or less was taken as an indicator of multi – collinearity. We dropped TG, LDL and VLDL from multivariate model to improve the tolerance.

RESULTS

A total of 626 patients presented with ACS during study period, out of which 215 had past history of ACS. Out of 411 new cases presenting with ACS, 88 subjects were excluded based on exclusion criteria and 323 subjects were included in the study (177-STEMI, 82-NSTEMI and 64-UA) as shown in Figure 1.

The baseline characteristics of the study subjects are summarized in Table 1. The study subject's age at the time of presentation varied from 26-86 years with a mean age of 58±12 years, and majority (58.80%) of study subjects belonged to 35-60 years of age. Majority (67.50%) of study subjects were male. Normal BMI was found in 66.25% study subjects with overweight and obese constituting 31.27%. History of smoking was found in 38.39% subjects, 14.24% were diabetics and 20.12% subjects were hypertensives. CK-MB was found to be raised in 79.75% subjects. Raised levels of serum cholesterol (9.58%), TG (25.23%), LDL (13.41%) and VLDL (26.51%) were found in study subjects respectively. Low levels of HDL were found in 87.85% subjects.

The magnitude of raised GGT among ACS was 41.80%. Median and interquartile range of serum GGT levels in STEMI, NSTEMI and UA were 39 (30-54) U/L, 45(28-76) U/L and 31(20.5-47.5) U/L respectively (Figure 2).

On univariate analysis odds of raised GGT were not statistically significant for age, BMI, smoking, DM, hypertension, CK – MB and lipid profile. Odds of raised serum TG [OR: 1.4 (95% CI: 0.84-2.34) \( P = 0.200 \)], raised serum VLDL [OR: 1.42 (0.85-2.36) (\( P =0.174 \))] and low serum HDL [OR: 1.38(0.68-2.82) (\( P =0.372 \))] were not significant correlates of raised GGT. Odds of raised GGT were [OR: 2.73 (95% CI: 1.39-5.47) \( P =0.003 \)] times high among NSTEMI compared to UA and increase in odds of raised GGT was statistically significant. However odds of raised GGT were [OR: 1.25 (0.68-2.31) \( P = 0.473 \)] times in subjects with STEMI compared to UA and increase in odds was not statistically significant. Final model derived by multivariate logistic regression suggested that the significant correlate of raised GGT were male sex [OR: 3.58 (95% CI:...
**DISCUSSION**

In this hospital based cross sectional study, from central rural India, we found the magnitude of raised GGT among subjects of ACS to be 41.80%. Table II shows results of previous studies.\(^{11-15,18-23}\) The differences in the prevalence could be due to different age groups, sample size, study design, reference range of GGT and difference in geographical area and subgroups of ACS.

Results of few studies showed significant correlation of raised GGT with increasing age in contrast to our study results.\(^{13,17}\) Statistically significant association of raised GGT in male patients with ACS in comparison to female patients was found, which were similar as reported by Puukka et al.\(^{24}\) Possible explanation for higher values in males could be higher prevalence of risk factors like smoking and alcohol in men and seminal vesicles as an extra source of GGT production in men. In our study, the association of raised GGT with increasing BMI was not statistically significant which was similar to a study conducted by Emiroglu.\(^{19}\) Results of studies conducted by Puukka et al.\(^{24}\) and Ruttman et al\(^{20}\) were in contrast to our study where significant association was found with BMI.

In earlier studies, it was found that increased GGT was associated with DM\(^{7-8,10,20-21,25}\) in contrast to our study results. In our study, significant association of GGT was not found in subjects with raised TG, chole-
terol, LDL and low HDL levels, however this, which was in contrast to various studies. In present study, subjects with NSTEMI had higher prevalence of raised GGT, compared to subjects with STEMI and UA, however this association was not statistically significant. Similar results were obtained by Turkish study done by Emiroglu. Major strengths of this study are adequate sample size, use of the standardized protocol and being the only study on association of GGT with ACS in central India specially referring to a rural population. Few studies reported that significant stenosis on coronary angiography; major adverse cardiac events (cardiovascular mortality) were independently associated with raised GGT level. This cross sectional study lacked the follow up analysis of cardiovascular event and mortality. Coronary angiography to prove the diagnosis of ACS could not be performed due to non-availability. We measured GGT levels only at presentation; there fore we have no data whether coronary revascularization and/or medical treatment can alter GGT levels. Lastly, this study was done on Indian population, so the results may not be applicable to other populations of different ethnicity. Alcohol consumption could be a confounding factor as reliability and validity of self-reported alcohol consumption is often questionable.

CONCLUSION

Our study concluded that GGT activity is increased in subjects with ACS. High levels of serum GGT on admission were associated with the burden of atherosclerosis in patients with ACS. As serum GGT is a cost effective and simple vascular risk marker, its routine measurement on admission may be helpful in determining high risk patients of ACS in clinical practice. Further studies with larger numbers of patients will provide more informative data on this subject.

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CONFLICT OF INTEREST

None.

ABBREVIATION USED

ACS: Acute coronary syndrome; BMI: Body mass index; CAD: Coronary artery disease; CIs: Confidence intervals; CK: Creatine kinase; DM: Diabetes mellitus; ECG: Electrocardiogram; GGT: gamma glutamyl transferase; HDL: High density lipoprotein cholesterol; LDL: Low density lipoprotein cholesterol; MI: Myocardial infarction; NSTEMI: Non ST elevated myocardial infarction; ORs: Odds ratio; STEMI: ST elevated myocardial infarction; TG: Triglycerides; UA: Unstable angina; VLDL: Very low density lipoprotein cholesterol.

REFERENCES


