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Original Research Article

Gamma glutamyl transferase as an atherogenic predictive marker in acute coronary syndrome

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ABSTRACT

Background: Acute coronary syndrome (ACS) remains a leading cause of mortality and morbidity world-wide. Atherosclerosis is the predominant cause of ACS and biomarkers that could detect vulnerable atherosclerotic plaque could potentially be of great value in identifying patients at risk of developing coronary events. The aim was to assess the role of gamma-glutamyl transferase (GGT) in atherosclerosis process. The objective was to compare serum levels of GGT in patients with ACS and control subjects, and also to find out the association between GGT and atherogenic risk factors such as diabetes mellitus, hypertension, dyslipidemia and smoking.
Methods: The design was a prospective case control study where a total of 151 patients, 100 ACS patients and 51 control subjects with the age group of 30-80 years were enrolled for the study. GGT was estimated by kinetic colour test using Beckman Coulter AU2700 analyser.
Results: The mean GGT levels of ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI) and unstable angina (UA) subgroups were 93.86, 87.87 and 29.27 U/L respectively, which showed statistical significant difference ($p<0.001$) when compared with control subjects 21.99 U/L. The higher GGT levels in ACS patients also correlated with angiographic diagnosis of atherosclerosis. No significant difference was noted in GGT levels among ACS subgroups having risk factors and without having risk factors.
Conclusions: Significantly higher GGT levels found in ACS patients reflects the burden of atherosclerotic changes and this association implies that GGT estimation can be used as an adjuvant biomarker that may help in identifying patients who are potentially at risk of coronary atherosclerosis.

Keywords: Acute coronary syndrome, Atherosclerosis, Gamma-glutamyl transferase, Risk factors

INTRODUCTION

Heart is the most dynamic organ in the human body which is responsible for keeping the blood circulating throughout the entire body system. The ailments of the heart are the most prevailing cause of death throughout the world and early diagnosis of the cardiac disease is a major drive area of medical research. Coronary artery disease (CAD), also known as Ischemic Heart disease (IHD) is the single leading cause of death worldwide. Coronary artery disease continues to be the major cause of disease burden and death in developed as well as in developing countries.[1,2] The prevalence of CAD, as well as the incidence of acute coronary syndrome (ACS) is very high among Indians, and in fact India has the maximum burden of ACS in the world.[3,4] The term acute coronary syndrome applies to a constellation of clinical signs and symptoms congruent with acute myocardial ischemia and covers the spectrum of clinical conditions ranging from unstable angina (UA) to non-ST-segment elevation myocardial infarction (NSTEMI) to ST-segment elevation myocardial infarction (STEMI).[5]

Atherosclerosis is the predominant cause of ACS and the majority cases are attributed to rupture of an atherosclerotic plaque in a coronary artery, resulting in the formation of a thrombus.[6] The resulting thrombus causes coronary artery occlusion and restricts the flow of blood to the heart muscle. Various mechanisms are associated with the pathogenesis of atherosclerosis in which oxidative stress and inflammation play significant roles.[7] In the modern era, use of cardiac specific serum biomarkers has become a contributory tool for diagnosis and management of patients with ACS. Many cardiac markers are available for clinical practice like cardiac troponins (Troponin-I and Troponin-T), creatine kinase-MB (CKMB), myoglobin etc. These cardiac markers are released in the serum during cardiac damage, but none of these markers detect the atherogenic burden before the major cardiac event occurs. Thus there is considerable on going interest and effort towards the identification of cardiac biomarkers which could be used for screening of individuals at risk of developing CAD or predict atherosclerotic coronary event.

Serum Gamma-glutamyl transferase (GGT) also known as gamma glutamyl transpeptidase is a second-generation hepatic function test which has been widely used as a diagnostic index of liver dysfunction, alcohol consumption and abuse.[8] GGT is the key enzyme accountable for the extracellular catabolism of glutathione (GSH), the chief antioxidant in mammalian cells. This degradation allows for precursor assimilation and recycling of amino acids for synthesis of intracellular glutathione. Meanwhile, the reactive thiol of cysteinyl-glycine moiety originated during GGT-mediated cleavage of glutathione on the cellular membrane or in the extracellular space may also cause the reduction of ferric (Fe^{3+}) to ferrous (Fe^{2+}) ion, thus starting an iron dependent redox-cycling process resulting in the production of the reactive oxygen species particularly superoxide anion and hydrogen peroxide, both capable of stimulating pro-oxidant reactions.[9] GGT mediated pro-oxidant reactions catalyse the oxidation of LDL lipoproteins (lipid peroxidation), likely contributing to the formation of inflammatory atheroma within the vascular endothelial wall.[10] Thus the oxidative stress mediated by GGT could play a central role in the pathogenesis of atherosclerotic plaque.[11] A number of clinical studies upon patients with coronary artery disease demonstrated that GGT activity was positively associated with oxidative and inflammatory reactions contributing to atheromatous plaque formation.[12,13] The positive relation between cardiac events and GGT levels remained significant even after modification of cardiac risk factors and possible confounders including alcoholism.[14,15] Therefore it has been put forward that GGT can be considered as a potent biochemical marker for preclinical development of atherosclerosis and the key advantages of GGT over other cardiac markers is its high sensitivity, accuracy and cost effectiveness.[16-18] Though the relationship between GGT and coronary artery disease has been reported by many research works, there are only few studies scrutinizing the variations of GGT in ACS patients, especially evaluating the levels of GGT in ACS subgroups, namely STEMI, NSTEMI and UA. The utility of GGT to detect atherosclerotic vascular process and thus its role as an early risk marker for identification of patients with acute events of coronary artery disease was focused in this study.

METHODS

The design was a prospective case control study conducted in a tertiary care centre. Based on the mean and standard deviation of GGT levels in the cases and controls from available literature and with 99.9% confidence and 99% power, minimum sample size came to thirty-five (35), i.e. 35 cases of ACS and 35 controls.[19] In the present study, hundred (100) patients who were admitted in the coronary care unit (CCU), cardiology department with a diagnosis of ACS, and undergone diagnostic coronary angiography were considered for the enrolment as cases. Fifty-one (51) subjects, who had no evidence of coronary artery disease, were enrolled as controls, and were selected from patients who came for regular health check-up.

The inclusion criteria for patients selected as cases were as follows

- Adult patients aged 30 to 80 years of either sex.
- Patients presenting with acute coronary syndrome.

Acute coronary syndrome was diagnosed based on the following criteria: for the diagnosis of STEMI, patients needed to have chest pain of greater than 20 minutes duration, with or without radiation to arm/jaw/back/ epigastrium, weakness, diaphoresis, nausea, light headedness with ECG changes of STEMI (ST-segment elevation ≥1 mm in two consecutive leads or left bundle branch block on presentation) and positive troponin values. For the diagnosis of Unstable angina, patient should have chest pain usually lasting for ≥20 minutes, or angina occurring with a crescendo pattern and ECG changes (ST segment depression ≥0.5 mm or T inversion ≥0.3 mv in any two leads) with negative troponin-I value. For the diagnosis of NSTEMI, apart from the above symptoms and ECG changes, the patient had elevated Troponin-I as a marker of myocardial necrosis.

The inclusion criteria for patients selected as controls were as follows

- Adult patients aged 30 to 80 years of either sex.
- Patients with no clinical and biochemical evidence of coronary artery disease.

Cases and control subjects also had any one or combination of coronary risk factors like diabetes mellitus, hypertension, dyslipidemia, or smoking history.

We excluded patients with any of the following

- Alcohol consumption
- Hepatitis B or C infection
- Other known hepatobiliary diseases or kidney disease
- Use of hepatotoxic drugs
- Pregnancy
- Documented malignancies.

Detailed history was taken and physical examination was done for all patients who were enrolled for the study. The blood pressure, body mass index (BMI) and medical history were recorded. The weight of each individual was measured using an electronic weighing scale; the height was measured with a wall-mounted stadiometer and arterial blood pressure with sphygmomanometer. Body mass index was calculated using the formula: BMI = Weight (kg)/Height^2 (m^2). Diagnostic coronary angiography was performed for all ACS patients by standard Judkins technique within the first 72 hours based on the clinical situation. Luminal narrowing ≥ 50% in at least one of the major coronary artery segment was considered as significant stenosis.

Venous blood was drawn from all enrolled patients under strict aseptic conditions at the time of admission from CCU. Overnight fasting venous blood was obtained for fasting plasma glucose and lipid profile estimation. Serum was separated by centrifugation at 3,000 rpm for 10 minutes, within one hour after blood collection and the parameters including GGT, Troponin I and lipid profile were estimated on the same day of collection of sample. Whole blood samples were used for testing glycated haemoglobin (HbA_1c) and plasma was used for testing glucose.Gamma glutamyl transferase was estimated by Kinetic colour test using Beckman Coulter AU2700 analyser. The cut-off value for GGT was taken as 55 U/L, as per assay kit. Troponin I was estimated by chemiluminescent micro particle immunoassay (CIMA) using Abbott Architect System. Fasting blood glucose was estimated by enzymatic UV test (hexokinase method) using Beckman Coulter AU2700 analyser. HbA_1c was estimated by ion-exchange high-performance liquid chromatography (HPLC) using Bio-Rad Variant™ II D-10 Hemoglobin A1c testing system. Total Cholesterol, HDL, LDL, and Triglycerides were estimated by enzymatic colour test using Beckman Coulter AU2700 analyser.

Statistical analysis

Data analyses were performed with the Statistical Package for the Social Sciences (SPSS) version 20 (SPSS Inc., Chicago, USA). All continuous variables were expressed as mean±standard deviation (SD), while categorical variables were expressed as number (percentage). The distribution of continuous variables for normality was tested with Kolmogorov-Smirnov test and analyzed for homogeneity using the Levene tests. Continuous variables were compared using independent sample student 't' test for two groups and analysis of variances (ANOVA) for more than two groups. Multiple comparisons between subgroups and controls were done using Bonferroni test. Categorical variables were compared using Chi-square test. A two-tailed p value <0.05 was considered as statistically significant.

RESULTS

The present study included one hundred fifty one patients, with 100 (77% males, 23% females) clinically and angiographically diagnosed acute coronary syndrome patients and 51 (56.9% males, 43.1% females) control subjects. Thirty six patients (88.9% males, 11.1% females) had STEMI, forty patients (70.0% males, 30.0% females) had NSTEMI and twenty four patients (70.8% males, 29.2% females) had UA.

Table 1: Comparison of demographic and clinical characteristics of the study population.

Variables	STEMI (36)	NSTEMI (40)	UA (24)	Control (51)	p Value
Age (years)*	57.69±11.73	63.03±11.07	64.00±10.02	50.80±09.45	<0.001
Gender					
Males#	32 (88.9)	28 (70.0)	17 (70.8)	29 (56.9)	0.016
Females#	04 (11.1)	12 (30.0)	07 (29.2)	22 (43.1)	
BMI (kg/m^2)*	28.72±4.21	27.43±5.12	26.56±4.78	25.37±3.57	0.062
Systolic BP (mmHg) *	127.78±22.44	137.50±25.99	142.08±22.26	132.75±18.77	0.068
Diastolic BP (mmHg) *	78.61±11.75	85.00±18.67	82.08±09.77	82.75±8.74	0.227
Diabetes mellitus#	20 (55.6)	26 (65.0)	10 (41.7)	20 (39.2)	0.067
Dyslipidemia#	22 (61.1)	23 (57.5)	12 (50.0)	17 (33.3)	0.038
Hypertension #	21 (58.3)	30 (75.0)	17 (70.8)	17 (33.3)	< 0.001
Smoking #	17 (47.2)	21 (52.5)	11 (45.8)	19 (37.3)	0.024

Variables denoted in ***** are expressed as mean ± standard deviation, and denoted in # are expressed as number (%), STEMI – ST elevation Myocardial Infarction, NSTEMI – Non ST elevation Myocardial Infarction, UA – Unstable angina, BMI: Body mass index

Table 2: Comparison of laboratory characteristics of the study population.

Variables	STEMI (36) (mean ± SD)	NSTEMI (40) (mean ± SD)	UA (24) (mean ± SD)	Control (51) (mean±SD)	p value
GGT (U/L)	93.86±3.21	87.87±3.06	29.27±3.89	21.99±2.86	< 0.001
Total cholesterol (mg/dl)	200.78±48.99	199.75±49.17	180.33±47.17	184.18±27.55	0.058
Triglycerides (mg/dl)	152.89±30.26	145.53±65.20	134.71±43.55	130.59±61.02	0.02
LDL C (mg/dl)	129.50±34.06	124.90±34.59	114.88±34.24	107.49±18.96	0.011
HDL C (mg/dl)	33.33±8.76	34.90±9.57	38.83±5.82	45.08±9.37	<0.001
FBS (mg/dl)	162.69±72.57	153.23±77.75	128.08±57.14	104.92±35.54	<0.001
HbA1c (%)	7.17 ±2.05	7.93± .69	7.08±2.19	6.96±2.09	0.055

Values are expressed as mean ± standard deviation, STEMI – ST elevation Myocardial Infarction, NSTEMI – Non ST elevation Myocardial Infarction, UA – Unstable angina, GGT – Gamma-glutamyl transferase, FBS – Fasting blood sugar, LDL C – Low density lipoprotein Cholesterol, HDL C – High density lipoprotein Cholesterol, HbA1c – Glycated hemoglobin.

Table 3: Comparison of mean GGT levels between patients with and without diabetes mellitus and dyslipidemia respectively among study subgroups.

Groups (n)	GGT (U/L) (Mean ± SD)		p value	GGT (U/L) (Mean ± SD)		p value
	With DM	Without DM		With DYS	Without DYS	
STEMI (36)	98.69±26.99	89.40±21.90	0.262	99.07±25.25	90.00±23.72	0.283
NSTEMI (40)	91.38±27.64	78.86±23.39	0.158	87.39±27.15	86.47±26.71	0.916
UA(24)	30.40±7.71	26.71±7.28	0.245	26.92±7.35	29.58±7.28	0.397
Control (51)	30.30±4.33	18.16±3.98	< 0.001	26.47±6.47	21.15±7.03	0.012

Values are expressed as mean ± standard deviation, STEMI – ST elevation Myocardial Infarction, NSTEMI – Non ST elevation Myocardial Infarction, UA – Unstable angina, GGT – Gamma-glutamyl transferase, DM – Diabetes mellitus, DYS – Dyslipidemia

Table 4: Comparison of mean GGT levels between patients with and without Hypertension and Smoking respectively among study subgroups.

Groups (n)	GGT (U/L) with HTN	(Mean ± SD) without HTN	p value	GGT (U/L) with smoking	(Mean ± SD) without smoking	p value
STEMI (36)	94.10±22.96	92.73±27.07	0.872	94.64±24.49	87.40±22.51	0.262
NSTEMI (40)	85.67±26.95	91.00±26.58	0.590	90.38±25.34	80.56±22.56	0.158
UA (24)	28.59±7.49	27.43±8.14	0.740	31.40±8.65	25.72±7.58	0.215
Control (51)	21.71±6.82	23.53±7.47	0.402	29.37±7.33	19.16±3.56	< 0.001

Among the controls 56.9% were males. There was a significant difference (p<0.001) in the proportions of males and females in the cases, as males are more affected than females. The mean age of presentation of STEMI, NSTEMI and Unstable angina were 57.69 yrs, 63.03 yrs and 64 yrs respectively and for control subjects the mean age was 50.80 yrs. Table 1 depicts comparison of demographic and clinical characteristics of the study population. In order to take care of the heterogeneity of variance, logarithmic transformation of GGT data was done for the analysis. The significant difference in age and gender were also considered when calculating mean and standard deviation of GGT among study population. The mean GGT levels of STEMI, NSTEMI and UA subgroups were 93.86 U/L, 87.87 U/L and 29.27 U/L respectively, which showed statistical significant difference (p<0.001) when compared with control subjects (21.99 U/L). Figure 1 demonstrates the mean GGT levels of ACS subgroups. As significant difference in the mean GGT was present, multiple comparisons using Bonferroni test was done which showed significant difference in mean GGT values between STEMI and UA (p<0.001), between STEMI and control (p<0.001), between NSTEMI and UA (p<0.001) and between NSTEMI and control (p<0.001). But there was no significant difference in mean GGT values between STEMI and NSTEMI and between UA and controls. Table 2 depicts comparison of laboratory characteristics of the study population. Out of the hundred patients diagnosed with ACS, 68% had hypertension, 57% had dyslipidemia, 56% had diabetes mellitus and 49% had smoking history. There were significant difference in the incidence of dyslipidemia, hypertension and smoking habit among study subgroups and controls, but there was no significant difference in the incidence of diabetes mellitus among them.

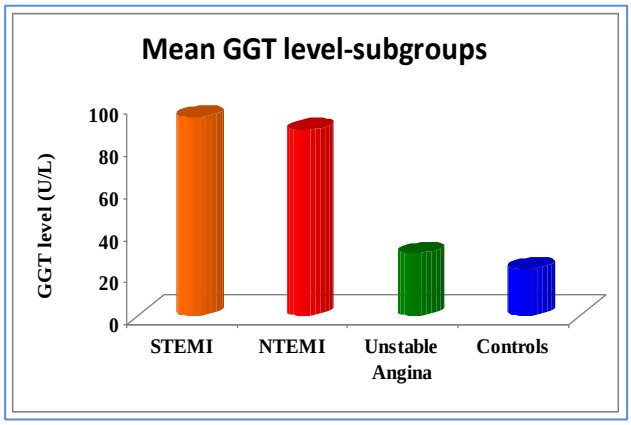

Figure 1: Mean GGT levels of study subgroups.

The comparison of mean GGT levels between cases and controls with and without risk factors (diabetes mellitus, dyslipidemia, hypertension and smoking) were done which showed no significant difference in GGT levels among ACS subgroups having risk factors and without having risk factors. But significant difference was noted in GGT levels among controls, as control subjects with diabetes mellitus, dyslipidemia and smoking history had high GGT level when compared with control subjects without these risk factors respectively. Table 3 and 4 depicts comparison of mean GGT levels between cases and controls with and without risk factors.

DISCUSSION

Acute coronary syndrome which comprises of acute myocardial infarction and unstable angina remains a leading cause of mortality and morbidity world-wide. There is a growing clinical interest among clinicians in the use of biochemical markers for screening individuals at risk of developing CAD, and researchers are constantly making efforts to find out newer biomarkers for the diagnosis of ACS at the earliest. The main cause of ACS is vulnerable coronary plaque due to atherosclerosis and biomarkers that could detect vulnerable atherosclerotic plaque could potentially be of great value in identifying patients at risk of developing coronary events. Lawton JS in his study mentioned that with regard to CAD there exist a significant sex differences between men and women.[20] Here in our study population also we noted a significant difference in the proportion of males and females affecting ACS, as the cases were predominately males, suggesting that males were affected more than females. The significant male predominance observed in the present study is in line with other studies done by El-Menyar et al[21] and Noureddine et al.[21,22] In the present study, the mean age of presentation of STEMI patients was 57.69 years who were slightly younger at presentation than those of NSTEMI (mean age-63.03 years) and UA (mean age-64 years) patients. The mean age at presentation of patients with STEMI in this study is comparable to the observations of CREATE registry data (57.5 years).[3] It was also noted that individuals from Indian subcontinent may develop coronary artery disease at a higher rate and at an early age.[23] In our study, the percentage of patients admitted with ACS less than 45 years of age was 09% and the youngest patient presented with ACS was 31 years old, signifying a very early onset of ACS and requiring an alarming attention.

In the present study, levels of serum GGT were measured in ACS patients (cases) and compared with that of control subjects who were life time non-alcoholics. We observed higher values of GGT among ACS subgroups, with more prominent elevation in STEMI followed by NSTEMI patients. Several studies have shown that circulating concentration of GGT were higher in patients with ACS than in those with healthy control subjects.[19,24] The higher difference with STEMI and NSTEMI groups than UA group proposes a relationship between GGT and severity of acute coronary syndromes.[19] Our ACS patients had significantly higher GGT levels that robustly correlated with angiographic diagnosis of atherosclerosis. Many clinical and epidemiological studies had revealed the independent role for GGT in the pathogenesis and clinical evolution of coronary artery disease brought on by atherosclerosis.[8,25] There is also evidence that atherosclerotic plaques contain GGT activity, revealed by many studies.[26,27] In human, GGT hydrolyses glutathione into cysteinyl-glycine dipeptide and glutamate. This dipeptide can serve as a reducing agent of iron and induce the occurrence of the super-oxide ion and hydrogen peroxide. As a result, GGT can trigger oxidative stress within atherosclerotic plaque and promotes atherosclerotic process by means of LDL oxidation in the vascular endothelial wall. These observations may enlighten the finding of an association between serum GGT levels and CAD risk prediction.

Although coronary angiography is currently the "gold standard" for diagnostic assessment of atherosclerotic lesions within coronary vessels, it is costly and invasive, and does carry a small risk of complication. Increasing evidence showed that among the non-invasive tests, GGT is emerging as an interesting cardiovascular risk marker for CAD, and GGT assay had shown acceptable diagnostic accuracy in our study also.[28] Many research works had observed that elevated GGT is an independent risk marker that predicts major cardiovascular events after modifying for other known cardiovascular risk factors as well as alcohol consumption.[13-15,29-32] Our study also clearly demonstrated that high serum GGT levels in individuals may not only attribute to alcoholism (as we excluded alcoholic patient), but also serve as an indicator of higher oxidative stress and inflammation, leading to atherosclerosis. In multi-speciality hospitals, techniques such as echocardiography, colour doppler and coronary angiography are utilized to detect vascular abnormalities resulting from atherosclerosis. Due to lack of availability of these sophisticated techniques in primary (PHCs) and secondary health care centres, morbidity associated with atherosclerotic changes still goes undetected, especially in view of the lower socio-economic status of the

population. In this scenario, as an easily available screening test, GGT could serve as an early predictor and trustworthy marker of sub-clinical atherosclerosis and its complications.

Dyslipidemia, diabetes mellitus, hypertension, smoking etc. are some of the risk factors for development of atherosclerosis.[33] Our study observed the high prevalence of conventional risk factors among ACS patients when compared with that of the control groups. Ninety five percentages of ACS patients presented with at least one of the four risk factors (hypertension, diabetes, dyslipidemia and smoking). This finding is in consistent with previous studies done by Rosengren at al.[34] Among control subjects, 66% of patients had at least one of the four risk factors. In our studied population, the most common risk factor among ACS patients was hypertension followed by dyslipidemia, diabetes mellitus and smoking. It was notable that hypertension, diabetes and smoking history were more common for NSTEMI, whereas dyslipidemia was more common for STEMI group.

Although several studies have been conducted demonstrating the enhancement of GGT activity in CAD patients, only limited information are available regarding the relationship between the GGT activity and well-known risk factors of CAD. Whether GGT levels were influenced by the presence of CAD risk factors was studied by comparing the mean GGT levels with respect to the presence or absence of the risk factors in both the case groups and controls, which observed no significant difference in the GGT levels between patients having risk factors and without having risk factors. These findings point out that although the role of risk factors in the process of development and progression of coronary atherosclerosis is well known, these risk factors didn't exert any prominent effect on the levels of GGT activity in patients with ACS, and the pro-atherogenic effect of GGT seems to be independent from these conventional risk factors. According to a prospective study on 6997 subjects, aged 40-59 years with no history of CAD or diabetes mellitus, and which was followed up for a period of 24 years revealed that the elevated GGT was significantly related with the increased risk of fatal CAD events and mortality, which was independent of the traditional CAD risk factors.[35]

Another major study on exploring the link between GGT activity and risk factors conducted by Meisinger et al concluded that serum GGT was a strong predictor of acute coronary events in apparently healthy men, independent of other risk factors for cardiovascular disease.[36] The significant difference in the GGT levels among control subjects with and without risk factors (diabetes mellitus, dyslipidemia and smoking history) point out that exist some relation between these risk factors and GGT. These findings were supported by few studies, which claimed a positive association between high serum GGT levels and recognized risk factors of CAD such as diabetes, hypertension and dyslipidemia.[37-39] To conclude about the influence of risk factors on GGT levels in the circulation, long term studies on a larger population are required. There are a few limitations associated with the present study. First, GGT assay sensitivity and specificity are unreliable for assessing atherosclerosis in patients with liver diseases and in alcoholics. Secondly, the study lacked the follow-up analysis of future cardiovascular events and mortality, which meant that the prognostic value of GGT level was not evaluated.

CONCLUSION

In conclusion, significantly higher GGT levels found in acute coronary syndrome patients reflects the burden of atherosclerotic changes occurred in these subjects. GGT activity rises as an indicator of increased oxidative stress in patients with CAD who have no liver disease or alcohol use. The association of GGT with CAD implies that, as an accurate and cost-effective test, GGT estimation can be used as an adjuvant biomarker that may help in identifying patients who are potentially at risk of coronary atherosclerosis and who may require early cardiac intervention. GGT assay can also be considered as a screening tool especially in primary and secondary health care centres to assess the burden of atherosclerosis before the decision to perform the costly and invasive procedures like angiography.

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