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A Study on Gamma Glutamyl transferase (GGT) in Non ST Elevation Acute Coronary Syndrome (NSTE-ACS) and its correlation with Angiographic severity and cardiac events

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KEYWORDS

Gamma Glutamyl Transferase, Acute Coronary Syndrome, Non ST Elevation Acute Coronary Syndrome

A B S T R A C T

The purpose of this study is to investigate the diagnostic value of Gamma Glutamyl transferase (GGT) in Non ST Elevation Acute Coronary Syndrome (NSTE-ACS) and its correlation with Angiographic severity and cardiac events. Coronary Artery Disease which is one of the leading causes of mortality and morbidity all over the world, has reached epidemic proportions worldwide recently in both Developed as well as Developing Countries. Coronary artery disease causes approximately 9.4% of total deaths in less developed countries and 16.3% of all deaths in well developed countries. Non ST Elevation Acute Coronary Syndrome and its Angiographic severity and cardiac events was studied in three groups depends on ACS Significant Stenosis and ACS non significant stenosis. In all three groups, the levels of Gamma Glutamyl Transferase enzyme in Non ST Elevation Acute Coronary Syndrome patients (both Unstable AnginaUA and NonST Elevation Myocardial Infarction NSTEMI) who were undergoing coronary angiogram and Control population of effort angina patients with normal coronary arteries by evaluation of atherosclerotic load. The serum levels of Median GGT values were significantly elevated in ACS patients with significant angiographic stenosis is in comparison with ACS without significant stenosis Serum GGT is an easily available, cost effective and simple biomarker marker, its routine measurement on admission may be helpful for identification of high-risk patients in clinical practice.

Introduction

Acute Coronary Syndrome (ACS) is a major part of chronic inflammatory athroscleotic coronary artery disease and it has evolved as a broad term that refers to spectrum of conditions compatible with acute myocardial ischemia and/or infarction that are usually due to sudden reduction in coronary blood supply[1]. The CREATE[2] registry has shown

that our country has the highest burden of ACS in the world. The absence of persistent ST-elevation is suggestive of NSTE- ACS. (except true posterior wall myocardial infarction) and it has been subdivided on the basis of cardiac biomarkers of myocyte damage (eg, CPK – MB, cardiac Troponin,) in to Unstable Angina and Non ST Elevation Myocardial Infarction (NSTEMI) in appropriate clinical conditions[1]. If cardiac biomarkers are elevated, the patient is diagnosed as NSTEMI[3]. Otherwise, the patient is considered to have Unstable Angina(UA). ST depression, transient ST-elevation, and /or prominent T-wave inversions may be present but are not must for diagnosis of NSTEMI. Abnormalities on the ECG and elevated troponins alone are not enough to diagnose the ACS but must be interpreted in the appropriate clinical scenario. Thus, UA and NSTEMI are closely related clinical scenarios whose pathogenetic mechanisms and clinical presentations are similar but vary in severity.

Gamma-glutamyl transferase (GGT) is an important enzyme found to be responsible for the extracellular catabolism of Glutathione[4] and has a unique role in oxidation of LDL cholesterol in the evolving atherosclerotic plaque and gradual progression of atherosclerosis in coronary arteries[5].

Epidemiologic studies have also reported that serum GGT levels have predictive and prognostic value for cardiovascular disease and mortality in the general population.

Similarly, GGT activity also has been demonstrated recently to be an independent risk factor for myocardial infarction (MI) and cardiac death in patients with documented coronary artery disease. The evaluation of the levels of low cost, easily available GGT in patients with NSTE-ACS, can be helpful for for investigating the association of GGT and coronary angiographic severity,major cardiac events as well as risk stratification & prognosis assessment in these group of patients

Materials and Methods

Chemicals

GGT kits were purchased from immune Diagnostic kits, USA and All the other chemicals used were of analytical grade.

Experimental Design

108 patients in the age group of 31-70 admitted in the intensive care unit of Meenakshi Medical College Hospital And Research Institute, Kanchipuram, Tamil Nadu, India for the study. This includes 75 male patients and 33 female patients with ACS significant stenosis and ACS non significant stenosis. The patients were divided into three groups are included,

Group- I - Control (Normal subjects)

Group-II – Acute chronic syndrome significant stenosis

Group-III- Acute chronic syndrome non significant stenosis

Ethical Concern

Ethical clearance was obtained from the Ethical committee meeting conducted at Meenakshi Medical College and Hospital.

Biochemical analysis

The activity of γ-glutamyl transferase was estimated according to the method of Orlowski and Meister (1965) modified by Rosalki and Rao (1972)

Cardiogram analysis

A 12 lead Electrocardiogram and Complete Echocardiogram including Doppler examination was performed.

Results andDiscussion

Gamma Glutamyl Transferase (GGT) In Acute Coronary Syndrome

In all three groups, median serum of GGT levels were significantly decreased in control groups when compared with Acute coronary syndrome groups. In our study shows the median of Gamma Glutamyl Transferase enzyme values were significantly elevated in NSTE - Acute coronary syndrome ($p<0.0045$) when compared with control polulation. The Median GGT values were significantly elevated in ACS significant angiographic stenosis($p<0.001$) compared with ACS with insignificant angiographic stenosis.

Table.1 shows the variation in median serum level of GGT during the study in the three different groups.

Gamma Glutamyl transpeptidase (U/L)	**ACS significant Stenosis**	**%**	**ACS Non Significant Stenosis**	**%**	**Control**	**%**
<25	1	1.28	28	93.33	45	100.00
26-35	27	34.62	2	6.67	0	0.00
>35	50	64.10	0	0.00	0	0.00
Total	78	100.00	30	100.00	45	100.00

Groups	Count	Sum	Average	Variance
ACS Significant Stenosis	78	2991	38.34615	47.86563
ACS Non Significant Stenosis	30	586	19.53333	14.74023
Control	45	688	15.28889	9.528283

ANOVA

Source of variation	SS	Df	MS	F	P-Value	F-crit
Between Groups	17768.28	2	8884.138	294.02	0.0045	3.056
Within Groups	4532.365	150	30.21577			
Total	22300.64	152				

Gamma Glutamyl Transferase (GGT) and vessel grades

Table 2: Shows the variation in median serum levels of GGT during the study in three different vessel disease condition. In our study, median serum GGT levels were significantly ($p<0.001$) decreased in control groups when compared with single vessel disease, double vessel disease and triple vessel disease condition.

GGT levels Vs Vessel Grades	Normal	SVD	DVD	TVD
< 25	28	1	0	0
26-35	2	24	3	0
>35	0	12	17	21
Total	30	37	20	21

GGT levels Vs Vessel Grades	Count	Sum	Average	Variance
Normal	30	586	19.53	14.74023
SVD	37	1255	33.9189	41.68769
DVD	20	822	41.1	27.46316
TVD	21	914	43.52381	11.1619

ANOVA

Source of Variation	Ss	df	MS	F	P-value	F-crit
Between groups	9108.174	3	3036.058	118.14	0.0001	2.691979
Within Groups	2673.262	104	25.70			
Total	11781.44	107				

Gamma Glutamyl Transferase (GGT) And Gensini Scores

Table 3: Shows the variation in median serum levels of GGT during the study in three different Gensini scores. The gensini score ranges were 51 -100, 26-50, < 25 in people who where having GGT values >35, 26-35, <25 U/l respectively. In our study, median serum GGT levels were significantly ($p<0.001$) increased in 26-50, 51-100 gensini scores when compared below 25 gensini scores.

GGT levels Vs Gensini	<25	26-50	51-100
<25	1	17	8
26-35	0	8	13
>35	1	27	50

GGT levels Vs Gensini	Count	Sum	Average	Variance
<25	1	12	12	0
26-50	27	682	25.25926	426.7373
51-100	50	2919	58.38	768.3629

ANOVA

Source of variation	SS	df	MS	F	P-value	F-crit
Between Groups	20426.02	2	10213.01	15.71395	0.002	3.118642
Within Groups	48744.97	75	649.9329			
Total	69170.99	77				

Gamma Glutamyl Transferase (GGT) And Adverse Events

Table.5 showed intra hospital outcomes for NSTE-ACS, as more number of adverse events (total of 18 events-Cardiogenic shock 3, arrhythmias 6, Heart failure 6 and Death 1) in significant stenosis subgroup in contrast to 2 events (arrhythmia 1, heart failure 1) in non significant angiographic stenosis subgroup. Mean GGT values were above 43 U/l in adverse events subgroup. P value was insignificant 0.81

Adverse Events	ACS Signicant Stenosis		ACS Non significant Stenosis	
	count	mean GGT Levels (U/L)	count	mean GGT Levels (U/L)
Cardiac Shock	3	44.67	0	0
Arrhythmia	6	44.33	1	20
Heart failure	6	43.67	1	22
Death	3	44.67	0	0
Chi Square Statistic		0.952		
Degree of Freedom		3		
P value		0.813		

Gamma Glutamyl Transferase (GGT) in acute coronary syndrome

In our study median Gamma Glutamyl Transferase enzyme GGT values were significantly elevated in NSTE - Acute coronary syndrome around 33.12 U/l vs control polulation around 15.3 U/l. (P Value 0.0045).

Median GGT values were significantly elevated in ACS significant angiographic stenosis of around 38.34 U/l in in comparison to 19.5 U/l in ACS with insignificant angiographic stenosis, P value 0.001.

In the present study the mean GGT levels were elevated in patients with NSTE-ACS

population than controls which was also correlating with degree of stenosis of caoronary arteries, left ventricular EF, Trop T and CPK-MB. These findings can be explained by means of GGT-mediated reactions influencing plaque evolution and rupture[5].

The present study concurs with study findings of Dogan et al[5] which found median GGT 32U/l in ACS vs 16U/l in effort angina group of patient and median GGT of 37 in significant stenosis subset versus 22 U/l insignificant stenosis subset on NSTE-Acute Coronary Syndrome population.our study finding are also supported by study by Emiroglu[6] et al, Demircan et al[7] and Ulus et al[8]. The Non ST elvation ACS occurs due to the disruption or erosion of the vulnerable plaques[9], usually associated with subtotal occlusion of the culprit arteries. These plaques include a big lipid core, also increased inflammatory activity, and a thin fibrous cap. There is clear evidence that atherosclerotic plaques contain increased GGT activity[10,11] and GGT oxidizes LDL cholesterol within the coronary plaques in the presence of Fe ions.

Therefore, GGT can trigger the vulnerability and evolution of the plaques in ACS evolution This findings have been supported by many large epidemiologic studies[5].

Our study has found such an elevation of GGTP, with more prominent elevation in NSTEMI patients GGTP was independently related to NSTE-ACS, as well as hypertension, smoking, and reduction of left ventricular EF. It is well-known that abundance of cardiovascular risk factors and low EF increase the likelihood of UAP&NSTEMI and risk of adverse cardiac events in patients presenting with chest pain.

Gamma Glutamyl Transferase (GGT) AND Vessel Grades

Our study examined the level of serum GGT in patients with NST- ACS ACS to estimate the load of atherosclerosis. Our findings indicate that high levels of GGT were associated with increased load of atherosclerosis in patients with ACS.

The angiographic findings in NSTE – ACS patient group were Single vessel disese of 47.5 %, Double vessel disease of 25 % and triple vessel disease of 27.5% (P value 0.000) Left main disease was found in 6.5 % of significant stenosis subgroup. (P value 0.15). Our study also found that median GGT greater than 30 U/l was useful for identifying the NSTE-ACS patients with significant stenosis, with a sensitivity and specificity of above 85%.

Gamma Glutamyl Transferase (GGT) and Gensini Scores

In our study, median serum GGT levels were significantly ($p<0.001$) increased in 26-50, 51-100 gensini scores when compared below 25 gensini scores. Our findings and GGT & Gensini correlation were also similar to Açikel et al73 study which found a significant relationship between serum GGTP levels and CAD extent and severity assessed by Gensini scoring in patients who underwent coronary angiography study for atherosclerosis burden evaluation with fatty liver correlation study

Recently Baktir AO et al[12] have evaluated GGTP activity and the CAD burden by SYNTAX score correlation in patients with STEMI. Although they found significant positive association between SYNTAX score and major adverse cardiac events, the study has failed to show any correlation

between serum GGT levels and Coronary lesion lesion complexity and severity by SYNTAX scores.

Gamma Glutamyl Transferase (GGT) And Adverse Events

In our study where we followed for intra hospital outcome evaluation for NSTE-ACS, the results were more number of adverse events (total of 18 events-Cardiogenic shock 3, arrhythmias 6, Heart failure 6 and Death 1) in significant stenosis subgroup in contrast to 2 events (arrhythmia 1, heart failure 1) in non significant angiographic stenosis subgroup.

The present study also correlates with recently conducted study in which over 600 ST Elevation Myocarial Infarction patients who were undergoing primary PCI were evaluated by Gul et al[13] for correlation of serum GGTP on admission and in hospital cardiovascular adverse events and mortality. They found that patients who were having high serum GGT more than 37 had higher risk of mortality and adverse cardiovascular events.

The present study also supported by GGT and major adverse cardiac events MACE studies done by Dogan et al[5], Apkek et al[14], Gul et al[13] and Lazzeri et al[15] in various groups of ACS.

Elevated serum GGTP level is an independent CV risk factor which predicts CV events, non-fatal Myocardial Infarction and mortality due to cardiac cause in unselected populations, in patients with history of MI, and in patients with ACS after adjusting for other CAD risk factors
In CAD population, serum GGT was associated with prognosis prediction independent of a variety of other established traditional risk markers. Even though the mechanisms linking GGTP and CV mortality have not yet been clearly demonstrated, various studies suggested that high GGTP levels were associated with high atherosclerosis burden which may explain the poor CV outcomes.

Statistical analysis

For statistical analysis, one way analysis of analysis of Variance (ANOVA) was used, followed by the Newman-Keuls Multiple Comparison test.

Conclusion

From the present study, to conclude, GGT levels can be increased in patients with NSTEACS, especially in Non STEMI, and identify those with significant coronary angiographic stenosis. Moreover, its relatively high levels can increase the risk of adverse cardiac events like cardiovascular events, non-fatal MI, and cardiac mortality in such patients 43-52. Thus, its measurement may be useful for prognostic evaluation of patients with NSTE-ACS independent of other established risk markers. As serum GGT is an easily available, cost effective and simple biomarker marker, its routine measurement on admission may be helpful for identification of high-risk patients in clinical practice.

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