

Levels of serum Gamma Glutamyl Transferase (GGT), high sensitivity C-Reactive Protein (hsCRP) in Myocardial Infarction (MI)-A case control study

Kavitha MM^{1,*}, Kashinakunti SV², Chandrashekharayya SH³, Manjula R⁴, Gurupadappa K⁵

¹Associate Professor, ^{2,3}Professor, ⁴Associate Professor, S. Nijalingappa Medical College & Sri Hanagal Kumareshwara Hospital & Research Centre, Bagalkot, Karnataka, ⁵Professor & HOD, Dept. of Biochemistry, Shimogga Institute of Medical Sciences, Shimogga

***Corresponding Author:**

Email: mekch@rediffmail.com

Abstract

Objectives: Acute myocardial infarction (AMI) is a major public health problem among non-communicable diseases in developing countries. Inflammation plays very important role in AMI. Gamma Glutamyl Transferase (GGT) has been used for years as an index of hepatic dysfunction, hepatobiliary system and marker of alcohol consumption. Recently studies demonstrated that increase in GGT activity can be used as oxidative stress marker and is involved in the pathogenesis of cardiovascular disease. Inflammatory marker i.e. high sensitivity C-reactive protein (hsCRP) is an acute phase protein, useful marker in AMI. Hence the present study was undertaken to estimate serum gamma glutamyl transferase activity, hsCRP levels in myocardial infarction (MI) patients and to compare with healthy controls and also to correlate between GGT, hsCRP with CK-MB levels.

Materials and Method: The study comprises of 100 subjects between age group of 30 to 70 years, 50 were diagnosed cases of myocardial infarction and 50 were healthy controls. Under aseptic precaution 5 mL of venous blood was drawn within six hours of admission and collected in plain vacutainer. Serum was separated and used for estimation of gamma-glutamyl transferase, hsCRP, urea and creatinine.

Results: Results were expressed as mean±SD. Student 't' test and Pearson correlation was applied. There was significant increase (p 0.001) in serum GGT activity, hsCRP and urea levels in MI patients compared to controls. There was also significant positive correlation between serum GGT, hsCRP and urea with CK-MB levels.

Conclusion: Our study concludes that GGT and hsCRP can be used as assisted biochemical marker in AMI patients along with other cardiac markers, which is simple and cost effective parameter in MI patients.

Keywords: Gamma glutamyl transferase, High sensitive C-Reactive Protein, Myocardial infarction

Received: 6th July, 2017

Accepted: 5th September, 2017

Introduction

Cardiovascular disease (CVD) have been attracting increasing attention because of increasing morbidity, mortality rates and threat to human health. CVD is the number one cause of death globally. Worldwide an estimated 17.5 million people died from CVD in 2012.⁽¹⁾ An estimated 2.33 million people died of CVD in India.⁽²⁾ Acute myocardial infarction (AMI) is one of the manifestations of coronary heart disease.

Gamma glutamyl transferase (EC- 2.3.2.2 □-glutamyl-peptide: amino acid gamma glutamyl transferase; GGT) catalyse the transfer of □ □-glutamyl group from peptides and compounds to an acceptor. It plays an important role in metabolism of glutathione.⁽³⁾ GGT is present in proximal convoluted tubule, liver, pancreas and intestine. The enzyme is present in cytoplasm (microsomes) but the larger fraction is located in the cell membrane.⁽⁴⁾

GGT was previously found to be an indicator of liver function, hepatobiliary tract diseases and alcohol consumption.⁽⁵⁾ GGT prepares precursor amino acid to intracellular glutathione (GSH) and catalyzes the first step in the degradation of extracellular GSH. As we know that GSH plays fundamental role in protection

against oxidative stress, in detoxification, metabolism of endogenous and exogenous compounds i.e. drugs and carcinogens. Role of GGT is to hydrolyze GSH hence degradation of GSH may play prooxidant role results in oxidative stress and cellular susceptibility to oxidant injury. Oxidation of low density lipoprotein cholesterol (LDL-C) through GSH/GGT dependent iron reduction has been suggested as an important mechanism in the pathogenesis of atherosclerosis.⁽⁶⁾ From the autopsy studies it is found that catalytically active GGT has been found on atherosclerotic plaque. It is believed that serum GGT is partially adsorbed onto LDL particles present in the plaque. GGT catalyze the oxidation of LDL hence contributing the oxidative events thus intern evolution of plaque and ultimately plaque rupture. Other than this GGT has important role in formation of fibrous cap, apoptosis of cellular elements of the lesion, plaque erosion and rupture, enhanced platelet aggregation and thrombosis. The expression of GGT is increased as an adaptive response upon exposure to oxidative stress.⁽⁷⁾

Recently it has been proposed that GGT is a potent biochemical marker for preclinical development of atherosclerosis.⁽⁸⁾ It is demonstrated that serum GGT

activity is an independent risk factor for myocardial infarction. Studies demonstrated that increase in serum GGT activity can be used as a marker for increased oxidative stress.⁽⁹⁾ The progress and prognosis of cardiovascular disease may be predicted by increasing GGT levels and cardiac mortality.^(10,11)

Inflammation plays an important role in AMI. Inherent to the inflammatory process is the occurrence of an acute phase response. This response is induced by pro-inflammatory cytokines, which are released from the inflamed tissue by inflammatory and parenchymal cells and thus stimulates liver to synthesize many acute phase proteins. Among them C-reactive protein (CRP) is classical acute phase reactant whose concentration is increased very much high.^(12,13) C-reactive protein belongs to pentraxin family. Data suggests that CRP level is a stronger predictor of cardiovascular events than low density lipoprotein cholesterol (LDL) and it adds prognostic information to that conveyed by the Framingham risk score. CRP is an index of inflammation that is now believed to promote directly all stages of atherosclerosis, including plaque rupture. Atherosclerosis has an inflammatory nature. High sensitive C-Reactive protein (hsCRP) is useful inflammatory and prognostic marker for cardiovascular disease.⁽¹⁴⁾ It is a biomarker of inflammation and as an independent predictor for CAD.

As there is paucity of literature regarding association of GGT and hsCRP in myocardial infarction patients. Hence the present study was undertaken to estimate serum levels of GGT, hsCRP and correlation of GGT & hsCRP with CK-MB in acute myocardial infarction patients.

Materials and Method

Study was conducted in the department of Biochemistry, S Nijalingappa Medical College and Sri Hanagal Sri Kumareshwara Hospital and Research Centre, Bagalkot, Karnataka, a tertiary care teaching hospital. Study protocol was approved by the Institutional ethics committee (IEC). Informed written consent was taken from all the participants or patient attenders. Study comprises of 100 subjects, 50 were known cases of acute myocardial infarction (MI) who are admitted in ICCU or medicine ward and 50 were age and sex matched healthy controls in the age group of 30-70 years without any previous history of chest

pain, diabetes mellitus, hypertension, alcoholics. Study was conducted from July 2015 to June 2016.

MI patients were selected based on WHO criteria i.e. typical retrosternal chest pain, abnormal ECG findings, and raised cardiac markers. Patients with non-cardiac chest pain, liver dysfunction and chronic alcoholic consumption, acute infectious diseases, recent surgeries, arthritis patients were excluded from the study.

Detailed family history and general physical examination was taken from patients and patient attenders. Under aseptic precautions 5 mL of venous blood was drawn on the day of admission within six hours. Blood was allowed to clot and serum was separated and used for estimation of following biochemical investigations. Serum CK-MB was estimated by immunoinhibition method, Troponin-I by fluorescence immunoassay method using Alere Triage kit. GGT was estimated by IFCC kinetic method, hsCRP by immunoturbidimetric method, urea by urease and creatinine by alkaline picrate method in fully automated analyser Biosystem A25 using Biosystem kits.

Statistical analysis: Data were collected and analysed using software Social Package Social System (SPSS) version 13. All results were expressed as mean \pm SD. Student "t" test was applied for comparison of two groups and Pearson correlation test was applied.

Results

Table 1 shows baseline characters of both cases and control group. Table-2 shows the cardiac markers among MI patients and controls. There was statistical significant increase ($p < 0.001$) in CK-MB and Troponin-I levels in MI patients compared to controls.

Mean values of GGT, hsCRP, urea and creatinine are shown in Table-3 among two groups. There was statistical significant difference in GGT, hsCRP and urea levels among two groups, but serum creatinine levels are increased among MI patients but it was not significant.

Pearson correlation was applied, there was significant ($p < 0.05$) positive correlation between CK-MB and GGT (Fig. 1) also significant ($p < 0.05$) positive correlation between CK-MB with hsCRP (Fig. 2) and urea (Fig. 3).

Table 1: Shows the baseline characters in MI patients and controls

	Cases	Control	p-value
Male : Female	31:19	28:22	-
Age in Year	61.6 \pm 15.4	58.78 \pm 11.94	NS
BMI Kg/m ²	24.37 \pm 5.18	25.68 \pm 6.5	NS
SBP mm Hg	128 \pm 14.36	112.4 \pm 8.6	< 0.05
DBP mm Hg	82 \pm 12.57	76 \pm 8.45	NS

NS-Non significant

Table 2: Mean values of CK-MB and Troponin-I in cases and controls

Parameters	Cases	Controls	p-value
CK-MB IU/L	82.54 ± 39.94	12.54 ± 5.03	0.001
Troponin-I ng/mL	5.9 ± 1.37	0.14 ± 0.05	0.001

Table 3: Showing GGT, hsCRP, Urea and Creatinine in cases and controls

Parameters	Cases	Controls	p-value
GGT I/L	39.26 ± 18.79	10.18 ± 5.72	0.001
hsCRP mg/L	3.82 ± 1.04	1.22 ± 0.35	0.001
Urea mg/dL	54.28 ± 33.31	19.16 ± 6.19	0.001
Creatinine mg/dL	1.48 ± 0.67	1.08 ± 1.13	0.39

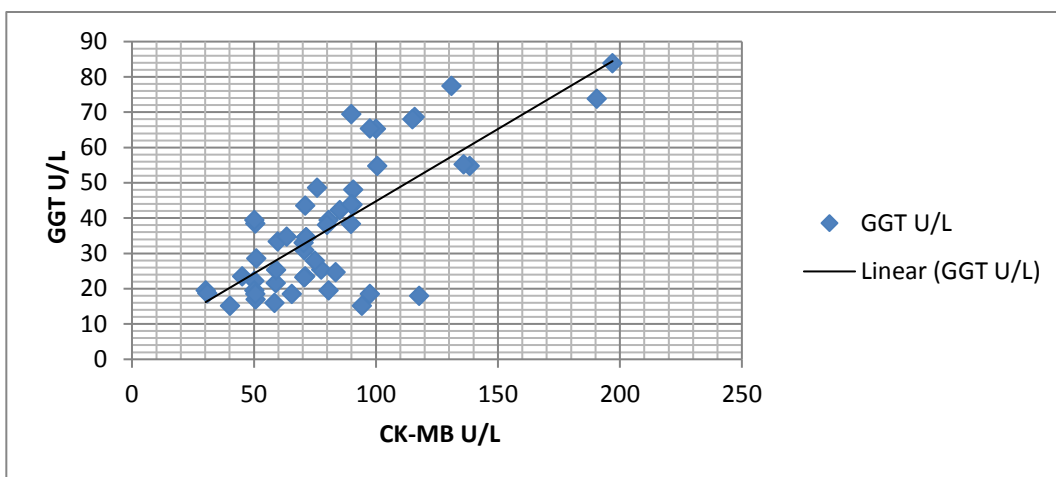


Fig.1: Correlation between CK-MB and GGT

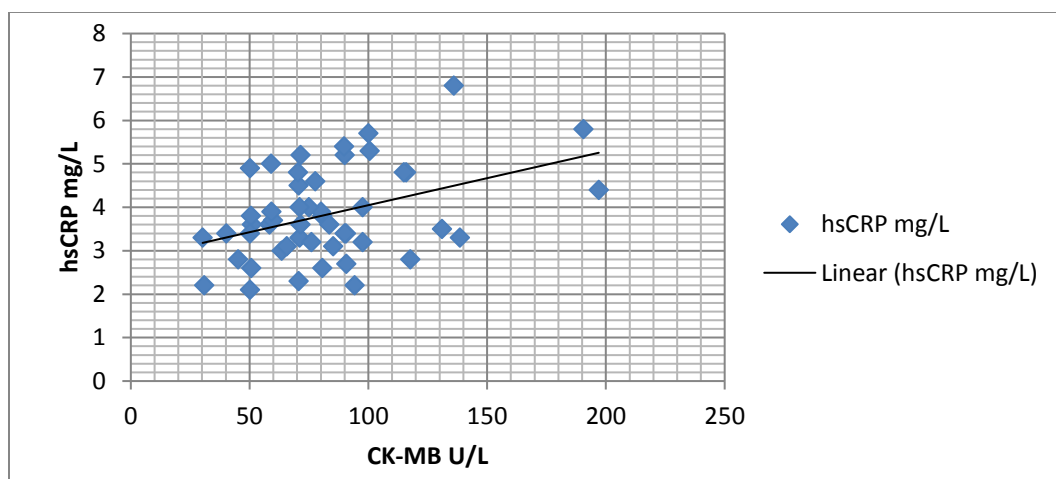


Fig. 2: Correlation between CK-MB and hsCRP

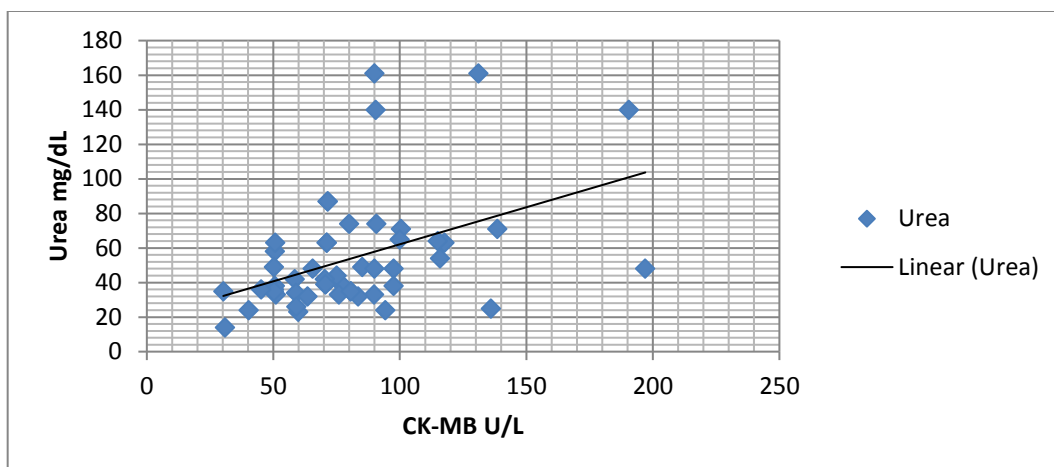


Fig. 3: Correlation between CK-MB and urea

Discussion

GGT act has an antioxidant. In our study there is significant increase in GGT levels in AMI patients compared to controls. A study by Ashishkumar⁽¹⁵⁾ et al from Vadodara, concluded that a significant elevation of GGT in AMI patients and it showed significant association with severity of AMI and positively correlates with CK-MB levels which is in accordance with our study. According to Michele Emdin⁽¹⁶⁾ et al, GGT is an independent risk factor in ischemic patients with established coronary atherosclerosis and previous MI. They also found positive correlation with lipid parameters and revealed that serum GGT activity is related to cardiac death.

In AMI there is increased oxidative stress hence there decreased glutathione levels. Decreased glutathione induce formation of GGT to maintain preexisting levels. A multicentric prospective epidemiological study⁽¹⁷⁾ on 5115 patients with coronary artery risk development in young adults (CARDIA) concluded that GGT is a sensitive early stage predictor of oxidative stress. A study done by Uygur⁽¹⁸⁾ et al, showed high admission GGT levels are associated with poor myocardial perfusion in acute MI undergoing primary percutaneous coronary intervention. According to few studies measurement of GGT may be useful in predicting the cardiovascular risk^(9,19) by Demircan S et al and Desai GM.

hsCRP act has an inflammatory marker by activating complement pathway, induces adhesion molecule expression by endothelial cells, recruitment of monocytes into the arterial walls.⁽²⁰⁾ It induces plasminogen activator inhibitor-1 expression and enhances phagocytosis hence these results in vascular endothelial injury.⁽²¹⁾

According to Emiroglu MY⁽²²⁾ et al a trial on 219 acute coronary syndrome patients concluded that serum GGT and hsCRP levels were higher in these acute coronary syndrome (ACS) patients. Increase GGT was more significant among NSTEMI, STEMI groups compared to UAP and controls. Study by Devaki⁽²³⁾ et

al, concludes that hsCRP levels could be used risk assessment, diagnostic and prognostic marker in myocardial infarction patients. There are many advantages in measuring hsCRP as it is a stable compound, can be measured at any time without regards to biological clock. It is a simple, easy and cost effective. Our study showed significant increase and positive correlation with CK-MB.

In our study there is significant increase in urea levels in MI patients compared to controls which is in accordance with other studies.^(24,25) Our study also showed positive correlation with CK-MB. Increased urea levels indicate renal response to systemic hypoperfusion with respect to reduced cardiac output in heart failure. Hence decreased clearance from kidney and retention in the blood leads to elevated blood urea levels. In our study there is increased serum creatinine in myocardial patients compared to controls but it was not significant.

Conclusion

Elevation of serum GGT activity hsCRP and urea has significant association and positive correlation with CK-MB. Increased hsCRP levels in AMI patients suggest involvement of inflammation in pathogenesis of MI and its potent prognostic role in AMI. Since, serum GGT and hsCRP are simple and cost effective biochemical test, can be advised in routine cardiac marker profile. So GGT and hsCRP can be used as assisted biomarker along with other cardiac markers in MI patients and also cardiovascular risk evaluation.

References

1. WHO (2014), global status report on non-communicable disease, 2014.
2. WHO (2002), Health situation in South East Asia region 1998-2000.
3. Meister A, Larsson A, Orrenius S et al. Metabolism and transport of glutathione and other g-glutamyl compounds, functions of glutathione: biochemical, toxicological and clinical aspects, Revan press 1983, New York.1-22.

4. Husbey NE, Multiple forms of gamma glutamyl transferase. Association of the enzyme with lipoproteins. *Clin Chim Acta*. 1982;124:103-12.
5. Whitefield JB. Gamma glutamyl transferase. *Crit Rev Clin Lab Sci*. 2001;38:263-355.
6. Emdin M, Pompella A, Paolicchi A. Gamma glutamyl transferase, atherosclerosis and cardiovascular disease: Triggering oxidative stress within the plaque. *Circulation*. 2005;112:2078-80.
7. Paolicchi A, Emdin M, Passino C et al. Lipoprotein and LDL- associated serum GGT in patients with coronary atherosclerosis. *Atherosclerosis*. 2006;186:80-5.
8. Okan T, Izzat T, Ahmet Gurkek. Association of gamma glutamyl transferase with cardiovascular risk: A prognostic outlook. *Archives of Medical research*. 2009;40:318-20.
9. Sabri D, Mustafa Y, Kenan D, Fethi K, Serdar D, Mesut P, Okan G. The importance of gamma glutamyl transferase activity in patients with coronary artery disease. *Clin Cardiol*. 2009;32(4):220-5.
10. Wannamethee G, Ebrahim S, Shaper G. Gamma glutamyl transferase; determinants and association with mortality from ischemic heart disease and all causes. *Am J Epidemiol*. 1995;142:699-708.
11. Ulas T, Yildirim A, Sade LE, Balta S, Ozin B, Sezgin A et al. Serum gamma glutamyl transferase activity: a new marker for coronary artery bypass graft disease. *Turk Kardiyol Dern Ars* 2011;39(3):205-13.
12. Merriman CR, Pulliam LA, Kampschmidt RF. Effect of leukocytic endogenous mediator on C-reactive protein in rabbits. *Proc Soc Exp Biol Med*. 1975;149:782-4.
13. Oliveira EB, Gotschlich C, Liu TY. Primary structure of human C-reactive protein. *J Biol Chem*. 1979;254:489-502.
14. Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. *Circulation*. 2002;105:1135-43.
15. Ashish kumar, et al. A study of serum GGT activity to assess severity in myocardial infarction. *IJBAR* 2013;4(9):585-91.
16. Emdin M, Passino C, Michelassi C, Titta F, Abbate L, Donato L Pompella A, Paolicchi A. Prognostic value of GGT activity after MI. *European heart journal* 2001;22:1802-7.
17. Lee DH, Jacobs DR, Gross M et al. GGT is a predictor of incident diabetes and hypertension: the coronary artery risk development in young adult (CARDIA) study. *Clinical chemistry*. 2003;49(8):1358-66.
18. Yaksel UC, Celik T, Celik M, Bugan B, Lyisoy A, Yaman H. High admission levels of GGT predict poor myocardial perfusion after primary percutaneous intervention. *Clinics* 2011;66(10):1729-34.
19. Desai GM, Raghunandan R, Dharapur MS, Merchant R, Rajeshwari K. Role of GGT in evolution of coronary artery disease. *Int J Curr Res Aca Rev* 2014;2(2):187-193.
20. Bhakdi S, Torzewski M, Klouche M, Hemmes M. Complement and atherogenesis: binding of CRP to degraded, non-oxidized LDL enhances complement activation. *Arterioscler Thromb Vasc Biol*. 1999;19:2165-8.
21. Fichtlscherer S, Rosenberger G, Walter DH, Breuer S, Dimmeler S et al. Elevated C-reactive protein levels and impaired endothelial vaso-reactivity in patients with coronary artery disease. *Circulation*. 2000;102:1000-6.
22. Emiroglu MY, Esen OB, Bulut M, Karapinar H, Kaya Z, AKcakoyun M, Kargin R, Aung SM. GGT levels and its association with hsCRP in patients with acute coronary syndrome. *North American Journal of Medical Sciences* 2010;July 2(7):306-10.
23. Devaki RN, Suma MN, Basavana Gowdappa H, Manjunath Goud BK, Bhavana nayal. hsCRP levels in myocardial infarction patients in relation to cardiac markers. *IJABPT*. April-June 2011;2(2):100-3.
24. Liong BK, Uleng B, et al. Blood urea nitrogen as predictor of mortality in myocardial infarction. *Universe Medicina*. Sep-Dec 2013;32(3):172-8.
25. Rakesh M, Shirang PK, Dhiraj JT, Vidya SP, Pramod SK. Association of serum electrolytes and urea levels with cardiac markers in AMI. *International J of Clinical Biochemistry and Research*. 2015;2(4):233-5.