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ORIGINAL ARTICLE

A CROSS SECTIONAL STUDY OF SERUM GAMAGLUTAMYL TRANSFERASE ACITIVITY WITH REFERENCE TO ATHEROGENIC LIPID INDICES IN PATIENTS WITH ISCHEMIC HEART DISEASE

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ABSTRACT: BACKGROUND: The incidence, prevalence, mortality and morbidity of ischemic heart disease are increasing all over the world. Early detection and prevention of ischemic heart disease is important. Hence, identification of biomarkers for cardiovascular disease and its risk factors is needed. **AIMS AND OBJECTIVES:** To evaluate the association of Gamaglutamyl transferase activity with lipid risk ratios in ischemic heart disease. **MATERIALS & METHODS**: This cross sectional comprises 50 healthy subjects and equal number of myocardial infarction cases. Serum gamaglutamyl transferase activity, lipid profile was estimated and lipid ratios were calculated. Data was statistically analyzed. **RESULTS**: Serum Gamaglutamyl transferase activity increased in myocardial infarction cases and is correlated with lipid ratios. **CONCLUSION**: Serum Gamaglutamyl Transferase activity may be used in clinical practice as an aid for prediction of ischemic heart disease.
KEYWORDS: Gamaglutamyl transferase; Atherosclerosis; Ischemic heart disease; Lipid ratios; Biomarkers.

INTRODUCTION: WHO has declared coronary artery disease as our modern epidemic. It is a very important public health problem. Cardiovascular disease accounts for 30% of deaths worldwide[1]. Epidemiological trends indicate that there would be an increase in incidence of cardiovascular diseases all over the world particularly developing countries. WHO predicts 11.1 million deaths globally and 71% death in developing countries due to coronary heart disease by 2020 AD[2]. The prevalence of coronary artery disease is constantly rising. The estimated global cost of cardiovascular disease was USD 863 million in 2010 and is expected to increase by 22% in next 20 years due to population ageing. India is in epidemiological transition. In addition to burden of endemic infections emerging threat of non-communicable diseases is a matter of concern. The incidence of cardiovascular disease has increased from 7% in 1970 to 32% in 2011. Ischemic heart disease is predicted to rise in India by 30-60% between 1990 and 2020. The current prevalence is 65.9 per 1000 males and 47.8 per 1000 females.

Ischemic heart disease is a condition in which there is an inadequate supply of blood and oxygen to a portion of myocardium. It typically occurs when there is imbalance between myocardial oxygen supply and demand[3]. The most common cause of myocardial infarction is atherosclerotic disease of epicedial artery. Atherosclerosis is thickening of coronary arterial walls due to deposition of lipids with reduction in lumen. The risk factors for above conditions are age, sex, family history, diabetes mellitus, hypertension, hyperlipidemia, cigarette smoking etc.[4] Research has shown that treatment of cardiovascular disease is difficult. Hence, the ability to prevent the development of

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cardiovascular disease is important. Serum markers of atherosclerosis and its risk factors for early detection and prediction of risk has gained much attention in recent years.[5]

Adverse lipid profile is one of the major risk factors of coronary artery disease and myocardial infarction. Dyslipidemia is a prominent and modifiable risk factor for cardiovascular diseases.[6] Dyslipidemia is manifested by elevation or attenuation of plasma concentrations of lipoproteins.[7] A traditional atherosclerotic lipid profile is characterized by high serum levels of cholesterol, triglycerides, low density lipoproteins and low levels of high density lipoproteins. The casual association between plasma lipid level and risk of atherosclerosis is well established.[8] Serum lipid levels are strongly correlated with coronary artery disease. Currently there is clear perception of the interrelationship between serum lipids, atherosclerosis and ischemic heart disease.[9]

The lipoproteins contribute to development of ischemic heart disease through lipid accumulation leading to vascular injury, atheroma and thrombus formation.[10] The variations of serum lipids from their normal levels can predict the development of coronary artery disease.[9] Intensive treatment of dyslipidemia stabilizes atherosclerosis and promotes its regression and reduces cardiovascular mortality in patients with coronary artery disease.[11]

In the absence of abnormal lipid profile the possibility of coronary artery disease cannot be ruled out.[11] Risk of coronary artery disease may be under estimated in some patients without typical dyslipidemia. Several indices have been derived from lipid profile to establish an index for predicting the risk of coronary heart disease. These lipid indices optimizes the predictive capacity of lipid profile.[12] They reflect balance between atherogenic and anti-atherogenic lipids.[13] They have greater correlation with coronary artery disease. Castelli's risk index, atherogenic index of plasma, atherogenic coefficient, cholindex are some of the lipid ratios used for predicting the risk of coronary artery disease in clinical practice.[14] Lipid ratios indicate dyslipidemia and risk of coronary artery disease. They are better predictors of coronary artery disease than lipids alone.

Gamaglutamyl transferase is an enzyme present in serum and plasma membrane of most cell types [15, 16]. Several prospective studies have shown a significant relation between elevated serum Gamaglutamyl transferase and subsequent development of myocardial infarction.[17] Serum gamaglutamyl transferase is associated with increased risk of myocardial infarction and cardiac death.[18] Cardiovascular epidemiology has recently highlighted a clear link between serum gamaglutamyl transferase and risk for myocardial infarction and cardiovascular death with evolution of atherosclerosis.[19 -22] There is increasing evidence linking raised gamaglutamyl transferase and cardiovascular risk factors like diabetes mellitus, hypertension, dyslipidemia.[23, 24] It has been shown to be a marker and risk factor for cardiovascular disease.[25] Elevated gamaglutamyl transferase may have adverse effects on lipid metabolism including hypercholesterolemia and hypertriglyceridemia, both considered as vascular risk factors.[26,27] Studies have shown that increased gamaglutamyl transferase is associated with unfavorable lipid profile.[28]

It is hypothesized that gamaglutamyl transferase activity has a role in causing serum lipid changes leading to atherogenesis and ischemic heart disease which can be predicted at early stage by lipid risk ratios. This study is conducted to evaluate the relationship of serum Gamaglutamyl transferase activity with lipid risk indicators in ischemic heart disease.

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OBJECTIVES:

1. To compare the serum Gamaglutamyl transferase activity, and lipid ratios in myocardial infarction patients and healthy subjects.
2. To correlate the serum Gamaglutamyl transferase activity with lipid ratios in myocardial infarction patients and healthy subjects.

MATERIALS AND METHODS: The research protocol was approved by M.R.Medical College's Ethical Committee. This analytical observational cross sectional study was carried out at Basaveshwar Teaching & General Hospital, Gulbarga, Karnataka for a period of one year from 01.11.2011 to 31.10.2012.

The study subjects were selected by simple random sampling. They comprised of 100 subjects divided into 2 groups – cases and controls. The cases group included myocardial infarction patients and healthy volunteers were included in control group. The study subjects were selected by the following inclusion and exclusion criteria. The patients between 30 to 60 years of age both sex and myocardial infarction were included for the study. Patients with history of cardiac risk factors, any systemic illness, recent surgery or trauma, endocrinal and nutritional disorders, pregnant women, drugs affecting lipid metabolism & alcoholics were excluded.

The equipment used for the study are BD vacutainers, syringes, Biohit Micropippettes, Remi Centrifuge and auto-analyzer Roche CIII auto analyzer. The reagent kits for biochemical estimations were obtained from Roche Diagnostics, Gmbh, Mannheim. The material used for this study consists of well-structured questionnaire and blood samples. Before participation, the volunteers were explained about the nature and purpose of the study. A voluntarily signed written consent was obtained from them.

A detailed history was obtained by the physicians and a complete physical examination was done with special emphasis on cardiovascular disease. Diagnosis of myocardial infarction was done based on ECG changes or rise in cardiac biomarkers. 2 ml of overnight fasting blood sample was collected aseptically from median cubital vein of each individual with a disposable plastic syringe with needle gauge No. 20 into a plain vacutainer. Blood was allowed to clot and then centrifuged at 4000 RPM for 15 minutes to obtain serum. The serum sample was subjected to the following biochemical estimations,

CKMB by Immunoinhibition IFCC method,
Troponin I by Immunochromatography card method,
Gamaglutamyl transferase activity by Szasz method,
Total cholesterol by CHOD-PAP method,
Triglycerides by GPO PAP ESPAS method,
HDL by Immunoinhibition method,
LDL by Homogeneous enzymatic assay.

The reference ranges of above parameters were,

Serum CKMB	0-24 IU/L
Serum Gamaglutamyl transferase activity	10-40 IU/L
Serum Total Cholesterol	150-200 mg/dL
Serum Triglycerides	50-150 mg/dL

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Serum HDL	35-70 mg/dL
Serum LDL	80-130 mg/dL

The atherogenic lipid ratios were calculated as follows:

Castelli's Risk Index-I (CRI) = TC/HDL_C

Castelli's risk index-II (CRII) = LDL_C/HDL_C

Atherogenic index of plasma (AIP) = $\text{Log } TG/HDL_C$

Atherogenic coefficient (AC) = $\frac{TC - HDL_C}{HDL_C}$

Cholindex = $LDL_c - HDL_C$ (TG<400)

= $LDL_c - HDL_C$ (TG>400)

The descriptive analysis of the data was done by mean and standard deviation. The comparison of parameters between cases and controls were done by unpaired 2-tailed t-test. $p<0.05$ was considered statistically significant. The association between dependent and independent variables was analyzed by Pearson correlation coefficient test. The statistical data analysis software SPSS Version-17 was used for Statistical analysis of the data.

RESULTS: The data from the above analysis were compiled into two tables i.e., Table-1 and Table-2.

Parameters	Controls	Cases	t-value	p-value	Significance
Age (years)	46.82±8.62	51.62±6.82	1.76	p >0.05	Not significant
Sex					
M	50	44	0.52	p >0.05	Not significant
Female	0	6	0.52	p >0.05	Not significant
GGT (IU/L)	15.32±3.43	32.32±12.07	6.92	p <0.001	Very highly significant
CR-I	15.33±0.90	4.00±1.00	4.54	p <0.001	Very highly significant
CR-II	1.90±0.60	24.0±0.80	5.22	p <0.001	Very highly significant
AIP	0.42±2.00	0.49±1.00	4.82	<0.001	Very highly significant
AC	2.39	3.98	3.56	p <0.05	Significant
CI					
TG<400	43.80	91.51	3.24	p <0.08	Significant
TG>400	62.90	122.52	3.68	p <0.08	Significant

Table 1: Comparison of Parameters in cases and controls

GGT = gamaglutamuyl transferase, CR-I = Castelli's risk index-I, CR-II = Castelli's risk index-II, AIP = Atherogenic index of plasma, AC = Atherogenic coefficient, CI = Cholindex.

Table-1 compares the mean value of the variables in healthy volunteers and myocardial infarction patients. The difference for age and sex were not statistically significant. Statistically significant differences were seen for gamaglutamuyl transferase activity, Castelli's risk index, atherogenic index of plasma, atherogenic coefficient and cholindex between the 2-groups.

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Lipid ratios	Controls (r value	Cases (r value)
Castelli's risk index-I	0.41	0.80*
Castelli's risk index-II	0.21	0.49
Atherogenic index of plasma	0.47	0.60*
Atherogenic coefficient	0.31	0.54*
Cholindex	0.33 0.36	0.48 0.52

Table-2: Correlation of GGT with Lipid Ratios in cases and controls

* = significant, GGT = gamaglutamuyl transferase.

Table-2 shows the association of serum gamaglutamuyl transferase activity with Castelli's risk index, atherogenic index of plasma, atherogenic coefficient and cholindex. The enzyme activity showed statistically significant correlation with the atherogenic lipid ratios (Fig 1 & 2).

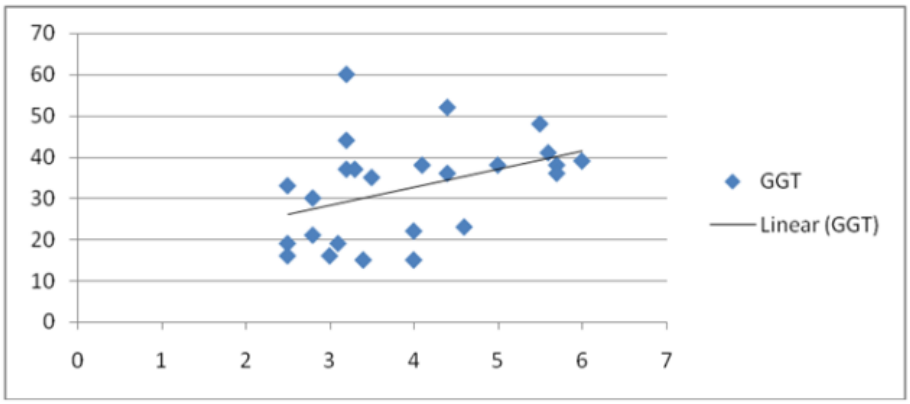

FIG. 1: Correlation of GGT with Castelli"s Risk index I in myocardial infraction

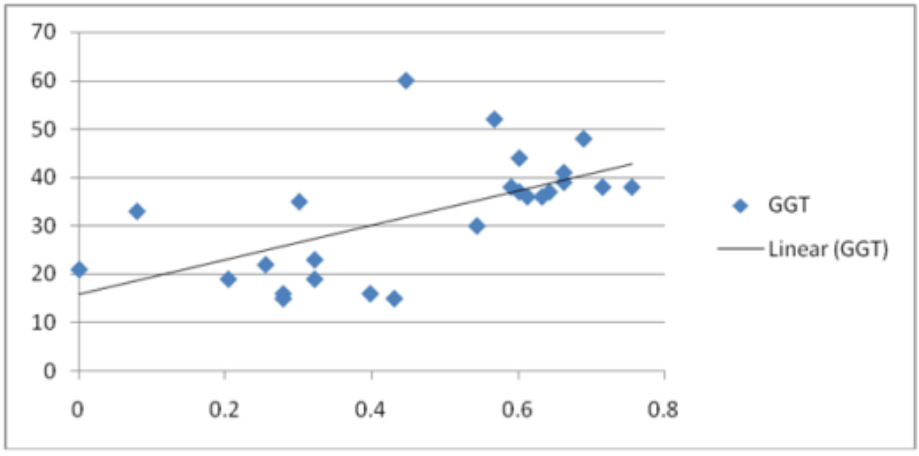

Fig. 2: Correlation GGT with AIP in myocardial infraction

DISCUSSION: The study was done to evaluate the relationship of serum Gamaglutamyl transferase activity with lipid risk indicators in ischemic heart disease.

In the present study, we have compared the values of Gamaglutamyl transferase activity and lipid ratios in healthy subjects and myocardial infarction patients. Also we correlated the Gamaglutamyl transferase activity with lipid ratios. We found increase in Gamaglutamyl transferase and lipid ratios in myocardial infarction patients and Gamaglutamyl transferase activity was associated with the lipid ratios.

Increased Gamaglutamyl transferase activity increases LDL oxidation forming oxidized LDL. The clearance of oxidized LDL from the body is slow. Thus increasing LDL and total cholesterol levels in blood[24, 25]. Increase in triglycerides levels decreases HDL levels. Increased low density lipoprotein and triglycerides cause atherosclerosis. Increased triglycerides, cholesterol, LDL and decreased HDL cause increase in values of lipid ratios. The findings of our study were similar to other studies done[26-28].

The strength of the work lies in standardized protocol, examination by experienced physician and biochemist. The limitations of the study, where the cross sectional study design, small sample size, subjects not sex matched, single measurements. The demographic and clinical data are lacking. Markers of inflammation, oxidative stress, endothelial dysfunction and coagulation were not done.

No conflict of interest was declared. All authors contributed in designing of study, collection, analysis, interpretation of data and manuscript preparation. We would like to thank the Dean, Medical Superintendent, Physicians, Former Biochemistry HOD Late Dr Jagdish B Ingin, Biochemistry teaching and non-teaching staff, patients and volunteers of Basveshwar hospital for their cooperation in carrying out the study.

We conclude that elevated Gamaglutamyl transferase activity though in normal range may increase risk of ischemic heart disease through lipid mediated atherogenesis independently of alcohol. Further studies need to be done on large scale to validate the test to use of Gamaglutamyl transferase in clinical practice as an aid for screening, prediction and early diagnosis of ischemic heart disease.

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