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Role of C-reactive protein and gamma-glutamyl transferase in the diagnosis of metabolic syndrome

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ABSTRACT

Previous studies have reported that metabolic syndrome (MetS) is associated with an increased risk of major cardiovascular events and levels of C-Reactive protein (CRP) can be considered as markers of MetS and its constituent components. Oxidative stress plays a major role in the development of MetS, and levels of gamma-glutamyl transferase (GGT) change with response to oxidative stress are also associated with MetS, which may be modulated by CRP. This study was conducted to identify the role of GGT and CRP as biomarkers in the diagnosis of MetS, a high-risk factor for cardiovascular diseases. One hundred and fifty patients meeting the diagnostic criteria of MetS and an equal number of controls were included in the study. The cases were selected from pathology and molecular biology laboratories, Karachi, while the controls came from the general population. Anthropometric indices of adiposity and blood pressure were recorded for both cases and controls. Blood samples were taken from all subjects to determine the levels of CRP and GGT. All those cases and control height, weight, hip waist circumference were noted and the comparison of CRP and GGT by applying students' t-test as markers for detection of metabolic syndrome. *p-value 0.001* was considered as significant. This study suggests that in patients with metabolic syndrome were found to have raised the basal metabolic rate, C-reactive protein and GGT were synergistically associated with MetS independently of another confounding factor in the general population.

Keywords: C-reactive protein (CRP), Gama glutamyl transferase (GGT), metabolic syndrome, (Met-S), inflammation, body mass index.

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Abbreviations: ALP, alkaline phosphatase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LFT, liver function test; TG, triglyceride, HDL, high-density lipoprotein.

INTRODUCTION

Metabolic syndrome (MetS) is a multifactorial disease that can cause a combination of health issues such as obesity, diabetes, hypertension, dyslipidemias, and insulin resistance. These individuals are at high risk of developing cardiovascular diseases. Early diagnosis and management are required to avoid these complications. This is associated with insulin resistance, increased body mass index, dyslipidemia which is characterized by an increase in plasma cholesterol, triglycerides (TGs), or both, and a low amount of high-density lipoprotein

cholesterol, all of which lead to atherosclerosis, hypertension, and macro-albumin-urea (Saklayen, 2018; Rochlani et al., 2017).

Although the MetS have recently been related to raised levels of CRP and GGT (Mahajan et al., 2012), some studies have found that those with GGT in the normal range have an increased risk of a variety of illnesses (Lee et al., 2009). In recent researches, the correlation is linked with metabolic abnormalities and other diseases with elevated levels of C-reactive protein (CRP) and gamma glutamyl transferase (GGT) (Wannamethee et al., 2008). It is reported that in recent years, associations have sparked interest in GGT as a marker of extra-hepatic diseases. High serum transaminases, serum alkaline phosphatase (ALP), GGT, and elevated triglyceride (TG) levels are the most common changes in the biochemical profile of these patients (Pardhe et al., 2018).

According to Adult Treatment Panel III (ATP III) or International Diabetic Federation (IDF), and frequently seen with metabolic syndrome but not included in the ATP III criteria are prothrombotic and proinflammatory tendencies (Sulistiowati and Sihombing, 2016). MetS is diagnosed based on central adiposity (increased waist circumference), raised triglycerides, low HDL, increased glucose and blood pressure. The presence of MetS raises the risk of cardiovascular disease and type 2 diabetes (Lee et al., 2020).

Abnormal circulating levels of hepatic enzymes are frequently found in hyperlipidemic patients. Ratziu et al. (2007) analyzed the relationships between serum levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT) and GGT and correlated them with cardiovascular and metabolic risk factors in a cohort hyperlipidemia patient; they discovered that 28% of individuals with abnormal ALT had high blood pressure, BMI, and blood glucose, total cholesterol, and triglyceride levels in their serum.

Because these irregularities may be linked to liver disease, more research is needed to pinpoint which hyperlipidemic individuals are at risk of severe liver damage (Kim et al., 2014). The highly sensitive C-reactive protein (hs-CRP), a well-known inflammatory biomarker, is a predictor of a variety of disorders, including cardiovascular disease and depression (Lee and Jacobs, 2005). C-reactive protein (CRP) and (GGT) are two independent risk factors for cardiovascular disease, as well as increased morbidity and death.

Although previous research has revealed that both GGT and hs-CRP are linked to metabolic abnormalities (Kawamoto et al., 2010), the degree of the link between GGT as an oxidative stress marker and hs-CRP independent of cardiometabolic concerns has yet to be determined. Our goal is to determine the relationship between GGT and subclinical inflammation (hs-CRP) and how this relationship changes with different levels of metabolic health.

The link association between GGT and cardiovascular disease is investigated, as well as the possibility of a link between serum GGT activity and Met S. It is also a potential association between GGT levels and cardiac risk with inflammatory marker CRP.

The purpose of this study is to employ a large aged population to expand the existing evidence base for GGT and CRP as alternative markers of metabolic disorders. We wanted to assess if there were any direct links between elevated levels of these biomarkers and dyslipidemia or hypertriglyceridemia in our population.

MATERIALS AND METHODS

All the samples were drawn from patients coming to Pathological and Molecular Laboratories as well as the control cases were also drawn from the Pathological and Molecular Laboratories. coming for the blood test and following the criteria of MetS. The patients and control cases included both the genders and their anthropometric indices of obesity and blood pressure were measured. C-Reactive Protein and Gamma Glutamyl Transferase levels were measured in all of the participants' blood samples.

This was a case-control study involving patients from all across Karachi who came to Pathological and Molecular Laboratories. From the general community, 150 patients who fit the diagnostic criteria for metabolic syndrome and an equivalent number of controls were chosen. The data was collected from January 2019 to December 2020. During our study, all the consent was shared with the participants and general parameters were asked and taken before collecting blood samples. Out of a total of 150 cases, all had MetS components to varying degrees, including hypertension, type 2 diabetes, impaired glucose fasting glucose, obesity, and dyslipidemia.

A commercial stadiometer was used to measure the height in cm and weight in kg with a digital scale was used. The waist circumference was taken at a position halfway between the ribs and the iliac crest. The BMI was computed by dividing the weight in kg by the height in meters squared. A mercury sphygmomanometer was used to measure systolic and diastolic pressures. After a 12-hour overnight fast, a 5ml blood sample was taken. Total cholesterol, LDL-C, and HDL-C levels were tested using Merck's Inuolin kit.

The GGT was quantified using an enzymatic colorimetric assay using L-γ-glutamyl-3-carboxy-4-nitroanilide as the donor substrate at 37°C. A Merck kit was used and examined with a Mindray Instrument. The CRP was measured quantitatively using an established turbidimetric assay (reagents Proline, Sweden) and the Oet-N10 multichannel analyzers kit.

Inclusion and exclusion criteria

All those patients with increased central obesity, systolic blood pressure, LFT with raised CRP and gamma-glutamyl transferase were included in the study with an equal number of controls. Patients with an altered LFT as a result of any other medical condition were not included in the study.

Data analysis

All of the data was imported into SPSS 25.0 and evaluated

quantitatively using the students' t-test. All the categorical data was interpreted as mean, and percentages (IBM Corp (2017). IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.)

RESULTS

Out of the 300 subjects in both the genders were enrolled, including 150 cases, meeting the diagnostic criteria of MetS and 150 were controls. There were 50 (33%) men and 100 (67%) women in the study, with a mean age of 68.44 years (range 60 to 85 years). The study was carried out in both genders and the general characteristics for the metabolic syndrome were determined. Table 1 presents the descriptive characteristics of the study population. The difference in mean values was tested using an independent sample t-test (Table 1). At the time of taking history, height and weight were also taken and blood pressure was noted before drawing the blood samples. Upon history smoking and alcohol consumption was more common in males. They were also found to have diabetes and cardiovascular disease and were on medication.

During this study female cases were also considered and on history, it was noted that they were also taking medicine for blood pressure and they were diabetic and dyslipidemia.

We assessed the clinical characteristics of study participants who had MetS against those who did not. It was observed that all the parameters were significantly higher in MetS subjects as compared to controls (p < 0.001) as shown in Table 2.

The inflammatory markers GGT and CRP were found to be considerably increased in metabolic syndrome patients when compared to controls (Table 3). Pearson's correlation coefficient was generated between CRP and GGT among metabolic syndrome cases and controls (Figure 1). Both CRP and GGT were positive and significantly associated with MetS (r = 0.587) as well as in controls (r = 0.120) when compared.

Table 1. Descriptive measures of study population, N = 150.

	M* ± *SD	**[95% CI]**	**Range**
Age, years	68.44 ± 8.04	[67.52, 69.35]	60 – 90
Anthropometric indices of obesity			
Weight, kg	62.47 ± 15.77	[60.68, 64.26]	38 – 134
Body Mass Index, kg/m^2	23.67 ± 5.84	[23.24, 24.34]	15.90 – 50.40
Waist Circumference, cm	84.42 ± 11.64	[83.10, 85.74]	63.50 – 152.40
Waist-Hip Ratio	0.88 ± 0.08	[0.87, 0.89]	0.69 – 1.23
Clinical examination			
Systolic BP, mmHg	131.27 ± 17.27	[129.30, 133.23]	100.0 – 180.0
Diastolic BP, mmHg	81.47 ± 11.76	[80.14, 82.81]	60.0 – 120.0
MAP, mmHg	98.07 ± 12.27	[96.67, 99.46]	76.67 – 136.67
Biochemical			
FBS, mg/dl	96.80 ± 27.79	[93.64, 99.96]	59 – 277
CHO, mg/dl	178.26 ± 50.80	[172.48, 184.03]	60 – 389
TG, mg/dl	136.88 ± 46.05	[131.65, 142.11]	45 – 288
LDL, mg/dl	118.76 ± 67.40	[111.10, 126.42]	29 – 477.2
HDL, mg/dl	38.77 ± 19.41	[36.56, 40.97]	24 – 126
SGPT, U/L	73.76 ± 58.52	[67.11, 80.41]	17 – 226
SGOT, U/L	73.80 ± 56.95	[67.33, 80.27]	12 – 214
ALP, U/L	248.64 ± 67.40	[240.98, 256.30]	118 – 456
GGT, U/L	42.81 ± 25.97	[39.86, 45.76]	13 – 99
CRP, mg/dl	10.50 ± 8.34	[9.55, 11.44]	1.2 – 28.2

Abbreviations: BP, blood pressure; MAP, mean arterial pressure; FBS, fasting blood sugar; CHO, cholesterol; TG, triglyceride; LDL, low-density lipoprotein; HDL, high-density lipoprotein; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic-pyruvic transaminase; ALP, alkaline phosphatase; GGT, gamma-glutamyl transferase; CRP, C-reactive protein; CI, confidence interval; SD, standard deviation.

Table 2. Comparison of diagnostic criteria of metabolic syndrome between cases and controls.

	MetS (n = 150)	Controls (n = 150)	
WC, cm	94.07 ± 13.73	82.42 ± 9.89	< .001***
FBS, mg/dl	105.36 ± 36.27	88.24 ± 9.31	< .001***
TG, mg/dl	156.68 ± 50.72	117.08 ± 29.89	< .001***
HDL-C, mg/dl	34.12 ± 6.54	43.42 ± 25.89	< .001***
SBP, mmHg	168 ± 17.61	120 ± 16.95	< .001***
DBP, mmHg	90 ± 12.55	76 ± 10.91	< .001***

Note: Values given as *M±SD,* mean ± standard deviation. Independent sample t test was used to compare means between subjects having MetS and Controls. *p < .05, significant; **p < .01, very significant; ***p < .001, extremely significant.
Abbreviations: MetS, metabolic syndrome; WC, waist circumference; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Table 3. Comparison of GGT and CRT between MetS cases and non-MetS controls.

	MetS (n = 150)	Controls (n = 150)	
GGT, U/L	64.72 ± 19.29	20.91 ± 3.98	< .001***
CRP, mg/dl	18.02 ± 5.01	2.97 ± 0.89	< .001***

Compare means between subjects having MetS and Controls. *p < .05, significant; **p < .01, very significant; ***p < .001, extremely significant.
Abbreviations: MetS, metabolic syndrome; GGT, gamma-glutamyl transferase; CRP, C-reactive protein.

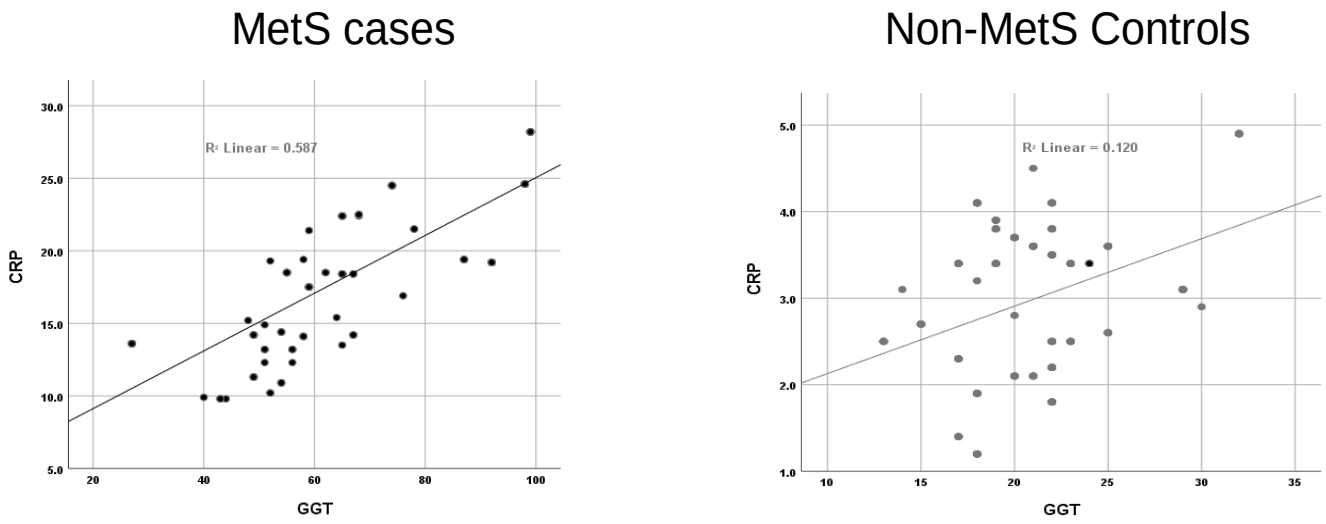

Figure 1. Comparison of the correlated graph between CRP and GGT in MS cases (r=0.587) and control cases (r=0.120).

DISCUSSION

The present study demonstrated the increased activity of GGT in MetS and high CRP, a marker for systemic inflammation. In the previous study, it has been demonstrated that serum GGT levels even within the normal range are associated with some atherosclerotic risk factors and are predictors of future heart disease (Wannamethee et al., 1995; Lee et al., 2003; Bozbaş et al., 2011).

In our study, we observed increased BMI, blood pressure, and liver enzymes (GGT, CRP) are all linked to metabolic syndrome, which increases the risk of cardiovascular disease and type 2 diabetes. When

compared to controls, the factors connected to MetS were considerably higher in this study. GGT and C-RP levels were also significantly elevated. Gamma-glutamyl transferase is a biomarker for hepatobiliary diseases. It promotes inflammation by assisting the conversion of glutathione-containing mediator leukoterine C4 to D4. Increased GGT levels have been linked to an increased risk of cardiovascular disease, diabetes, and metabolic syndrome (Lee and Jacobs, 2005). Hypertension, ischemic heart disease, congestive cardiac failure, and cardiac arrhythmias are examples of cardiovascular diseases. Elevated GGT was independently linked with the risk of 3-year all-cause mortality in individuals with diabetes and CAD (Lee et al., 2007; Ndrepepa and Kastrati, 2016; Mason et al., 2010; Kunutsor et al., 2015; Ndrepepa et al., 2016). CRP is an inflammatory blood measure linked to an elevated risk of cardiovascular disease and metabolic syndrome (Ndrepepa et al., 2016; Melvin et al., 2012).

Gamma-glutamyl transferase (GGT) is an enzyme located on the external surface of cellular membranes. It helps to maintain physiological cytoplasmic glutathione concentrations and cellular defense against oxidative stress by cleaving extracellular glutathione and increasing the availability of amino acids for intracellular glutathione synthesis. Increased GGT activity is a sign of deficiency in antioxidants and oxidative stress. Many research reported that elevated GGT activity is linked to an increased risk of cardiovascular diseases (CVD) such as coronary heart disease (CHD), stroke, arterial hypertension, heart failure, cardiac arrhythmias and all-cause and CVD-related mortality.

In a previous study, the exact mechanism of gamma-GT activity with cardiovascular diseases has yet to be established. But the most important mechanisms proposed for the relationship between gamma-GT and cardiovascular disease is the effects of gamma-GT on oxidative stress and glutathione mechanism. The activity of GGT has been detected within the atheroma plaque of carotid and coronary arteries, and gamma-GT found in the atherosclerotic plaques has been suggested to play a role in the formation and rupture of the plaques via catalysis of the oxidation of LDL (Emdin et al., 2005; Bozkus et al., 2016).

The evidence for an association between high GGT activity and acute ischemic episodes and myocardial infarction is weaker. The close relationship between GGT and traditional CVD risk factors and comorbidities, such as non-alcoholic fatty liver disease, alcohol consumption, oxidative stress, metabolic syndrome, insulin resistance, and systemic inflammation, may explain the risk of CVD or CVD-related mortality mediated by GGT (Ndrepepa et al., 2018). The discovery of GGT activity in atherosclerotic plaques, as well as a correlation between intra-plaque GGT activity and histological markers of plaque instability, may point to GGT's role in the pathogenesis of CVD, particularly atherosclerosis. However, it is unclear whether GGT plays a direct role in the pathogenesis of CVD or is an epiphenomenon of concomitant CVD risk factors or comorbidities, and Hill's criteria for a causal link between GGT and CVD have not been met.

In a further study, Lee DH and Jacobs DR Jr. reported that GGT was weakly correlated with CRP and in prior studies, CRP did not abrogate the predictive value of GGT for clinical events (Lee et al., 2007; Lee and Jacobs, 2005).

Future studies should investigate whether GGT provides prognostic information in addition to that provided by known cardiovascular risk factors for CVD or CVD-related outcomes, as well as the molecular mechanisms of GGT involvement in the pathophysiology of CVD and the eventual use of interventions to reduce circulating GGT activity (Lee et al., 2020). Ren et al. (2010) found in the Chinese population that high GGT was an independent risk factor for diabetes and that the effect of elevated CRP on diabetes was mediated by obesity. These markers were found to be predictive of the risk of disorders usually linked with altered metabolic profiles in the current investigation (Ren et al., 2010). GGT levels in the blood predict the start of metabolic syndrome, CVD, and death, implying that GGT is a metabolic and cardiovascular risk marker.

CONCLUSION

In conclusion, the current investigation found that high CRP and GGT levels in the general population are closely linked to MS or its components. In previous investigations, GGT and CRP were found to be linked to aberrant metabolic profiles. These markers were found to be predictive of the risk of disorders usually linked with altered metabolic profiles in the current investigation. We also looked into possible links between GGT levels in the blood and cardiac risk factors, as well as the levels of other liver enzymes and C-reactive protein. Intervention studies to see if lifestyle modifications can lower GGT and CRP levels might be beneficial in this area. More study is needed in this area to better understand the mechanism underlying the association between these routinely used indicators, disrupted metabolic profiles, and the risk of acquiring diseases like CVD and cancer.

Research highlights

These parameters were considered in this study because there were many cases in which it was not known why the inflammatory marker (CRP) was high with GGT, a biomarker for hepatobiliary diseases in elderly patients with Metabolic syndrome, and a comparison was made

with non-metabolic syndrome cases of the same age and lifestyle.

Limitation

We also sought to test glycosylated hemoglobin for diabetes confirmation in this investigation. We also intended to detect other inflammatory markers, but due to a shortage of funds, we were unable to do so.

Conflict of Interest

The author declares that they have no conflict of interests.

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