

# Serum GGT and serum ferritin as early markers for metabolic syndrome

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## ABSTRACT

**Background:** In India, the prevalence of lifestyle diseases like diabetes, hypertension, and metabolic syndrome (MetS) is showing an upward trend. Gamma glutamate transferase (GGT) and ferritin increase oxidant stress in the body through their role in glutathione homeostasis and iron metabolism, respectively. The increase in oxidant stress increases the inflammatory load, a risk factor for metabolic syndrome. These parameters are cheap, patient-friendly, and available in routine diagnostic labs compatible for follow-up, relieving the already overburdened healthcare system. **Methodology:** In a case-control study, samples of 77 cases of metabolic syndrome and 77 age and sex-matched controls were analyzed for serum GGT (by modified IFCC) and serum ferritin (by CLIA). Statistical analysis was done by SPSS 20.0 version. **Results:** The mean  $\pm$  SD for ferritin and GGT were  $101.58 \pm 84.20$  ng/dL and  $36.67 \pm 26.40$  IU/L, respectively in cases, whereas in control group these values were  $38.38 \pm 29.26$  ng/dL and  $16.53 \pm 6.79$  IU/L ( $P < 0.001$ ). Positive and significant correlation was seen between GGT with TG (r-value- 0.376/P-value-0.001) and GGT with waist circumference (r-value- 0.298/P-value- 0.022). A positive and significant correlation was seen between GGT and ferritin in cases with an r-value of 0.307 (P-value - 0.01). **Conclusion:** The increased values of GGT and ferritin in cases suggest an inflammatory load. The positive and significant correlation between GGT and triglyceride indicates its role in increasing oxidants' stress leading to inflammation and the development of MetS. The association of ferritin with MetS though insignificant may be considered as a biomarker.

**Keywords:** Biomarkers, lifestyles diseases, oxidant stress

## Introduction

The metabolic syndrome (MetS, Syndrome X, insulin resistance syndrome) is a constellation of several cardiovascular risk factors promoting atherosclerotic cardiovascular disease (ASCVD). Atherogenic dyslipidemia results in elevated blood pressure, triglycerides, glucose, prothrombotic, and proinflammatory states and low HDL- cholesterol.<sup>[1]</sup> Metabolic syndrome is associated with a 2-fold risk of CVD and a 5-fold risk of diabetes.<sup>[2]</sup>

Gamma-glutamyl transferase (GGT) has been regarded as a biomarker of hepatobiliary disease and alcohol abuse.<sup>[3]</sup> GGT is secreted by extrahepatic tissues, including kidney, epididymis, fibroblasts, lymphocytes, and lung.<sup>[4]</sup> GGT has a vital role in the extracellular catabolism of glutathione, the principal thiol antioxidant in humans. GGT enhances the availability of cysteine to promote intracellular glutathione (GSH) resynthesis, thereby counteracting oxidant stress.<sup>[5]</sup> It is expressed in the atheromatous core of coronary plaques where it colocalizes with oxidized low density lipoprotein (LDL) and foam cells.<sup>[6]</sup> GGT can be a proinflammatory marker as it mediates the interconversion of the glutathione-containing inflammatory mediator leukotriene C4 into leukotriene D4.<sup>[7]</sup> In a review article by Malnick *Set al.*<sup>[8]</sup> GGT was concluded as a predictive marker for MetS, CVD, and heart failure.

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Ferritin plays a crucial role in the regulation of iron homeostasis and is an accepted biomarker to evaluate body iron stores<sup>[9]</sup> Elevated serum ferritin levels have been demonstrated to predict type 2 diabetes mellitus in several studies<sup>[10,11]</sup> independently. In cross-sectional studies, high ferritin levels have been associated with hypertension, dyslipidemia, elevated fasting insulin and blood glucose levels, and central adiposity.<sup>[12]</sup> Lianlong *Y et al.*<sup>[13]</sup> in their study found that serum ferritin was positively correlated with different indices of MetS except for high-density lipoprotein cholesterol (HDL-C).

Gamma-glutamyl transferase (GGT) and ferritin participate in standard pathophysiological processes, including oxidative stress and lipid peroxidation. They are essential for the pathogenesis and the development of insulin resistance leading to metabolic syndrome.<sup>[14]</sup> The synergistic association of GGT and ferritin with inflammatory conditions can be a potential mechanism for the development of MetS.

In the Indian population, there is a rise in noncommunicable diseases like DM, HTN, CVD, etc., and with inadequate health resources available, it is highly essential to have some routine laboratory parameters for the prediction of metabolic syndrome. Ferritin and GGT are easily available at the primary care level and can be utilized as cheaper tests for risk assessment in MetS. In this study, the relationship between these conventional biomarkers and the metabolic syndrome was explored.

## Materials and Methods

It was a case-control study done at AIIMS Raipur. Ethical clearance was obtained from the Institute Ethics Committee for this study. Written consent was taken from all participants in this study. One hundred and fifty-four subjects were included in this study. They were classified into two main groups:

**Group I “Case group”:** It included 77 patients with a mean age of 41.15 years. Diagnosed as a patient with metabolic syndrome based on The US National Cholesterol Education Programme Adult Treatment Panel III (NCEP/ATP III) guidelines (2005).

NCEP/ATP III guidelines (2005) includes any three of the five criteria mentioned below :

Waist circumference- >40 inches (M), >35 inches (F).

Triglycerides-  $\geq 150$  mg/dL or on treatment.

HDL- <40 mg/dL (M), < 50 mg/dL (F) or on treatment.

Fasting glucose-  $\geq 100$  mg/dL or on treatment.

Blood pressure (BP) - >130 mmHg systolic or >85 mmHg diastolic or on treatment.

Individuals with a previous history of CAD, thyroid disorders, Cushing syndrome, familial hypercholesterolemia, pregnant and

postmenopausal females, chronic alcoholic, individuals on an iron supplement, and any hemoglobinopathies were excluded from the study.

**Group II “control group”:** 77 clinically healthy individuals with a mean age of 36.59 years. These individuals were attending AIIMS, Raipur for a routine check-up or were attendants of patients who are willing to be part of this research

Proper medical history and anthropometric parameters were measured in all the study subjects. The blood sample was collected after an overnight fast.

Following lab investigations were done on the samples:

- Serum GGT- Mod IFCC method
- Serum glucose- GOD-PAP (POD) method
- Serum triglycerides- GPO-PAP method
- Serum HDL-precipitation method

Above mentioned tests were done on Beckman Coulter AU system.

- Serum ferritin levels – CLIA method on ADVIA Centaur XP system

## Statistical analysis

The results were statistically analyzed by SPSS 20.0 for Windows. All the continuous variables were presented as mean  $\pm$  SD. Intergroup comparison was made by one-way ANOVA. The associations between the variables in a group were analyzed using the Pearson test as the correlation coefficient ( $r$ ) and their significance ( $P$ -value). Results were considered significant when the  $P$  value was  $< 0.05$ .

## Results

The present study was a case control study, comparing different variables amongst metabolic syndrome patients and age-sex matched controls, to establish the role of GGT and ferritin as biomarkers of early diagnosis.

Table 1 shows the association of different parameters of metabolic syndrome in the case and control group. An increased level of GGT and ferritin was observed in group 1 (cases) as compared to group 2 (controls) and the difference was statistically significant ( $P < 0.001$ ).

Both the sexes were almost equally represented in the study group 1, male = 54.24% and female = 45.76%

A significant positive correlation was seen between GGT and TG in cases, whereas in control the association was positive but insignificant [Table 2].

No significant association was seen between ferritin and any parameter of diagnostic criteria [Table 3].

**Table 1: Distribution of different variables amongst the study groups**

Variables	Gp-1 (n=77) Mean±SD	Gp-2 (n=77) Mean±SD	P	Biological Reference Interval
Age (years)	41.15±7.32	36.59±7.99	0.002*	
Waist Circumference (inches)	40.59±4.69	35.17±3.03	< 0.001*	
FBS (mg/dL)	164.65±69.08	91.47±7.99	< 0.001*	70-120
TC (mg/dL)	198.47±54.40	148.86±31.55	< 0.001*	<200
TG (mg/dL)	275.07±158.18	89.26±35.92	< 0.001*	<150
HDL-C (mg/dL)	37.13±10.66	43.89±9.2	< 0.001*	>50- M, >60- F
LDL-C (mg/dL)	108.37±48.85	89.26±35.92	0.01*	< 100
GGT (IU/L)	36.67±26.40	16.53±6.79	< 0.001*	9-58
FERRITIN (ng/mL)	101.58±84.2	38.38±29.26	< 0.001*	10-220

\*statistically significant

**Table 2: Correlation of serum GGT with different parameters of MetS in the study groups**

	Gp-1 r/P	Gp-2 r/P
FBS	0.082/0.499	-0.112/0.691
TG	0.376/0.001*	0.271/0.277
HDL-C	0.024/0.842	0.048/0.851
Waist Circumference	0.298/0.022*	0.008/0.954

**Table 3: Correlation of Serum Ferritin with different parameters of MetS in the study groups**

	Gp-1 r/P	Gp-2 r/P
FBS	-0.113/0.360	0.351/0.167
TG	0.217/0.074	0.197/0.420
HDL-C	0.066/0.590	-0.267/0.691
Waist Circumference	0.184/0.162	0.208/0.116

**Table 4: Correlation between Serum Ferritin and Serum GGT in the study group 1**

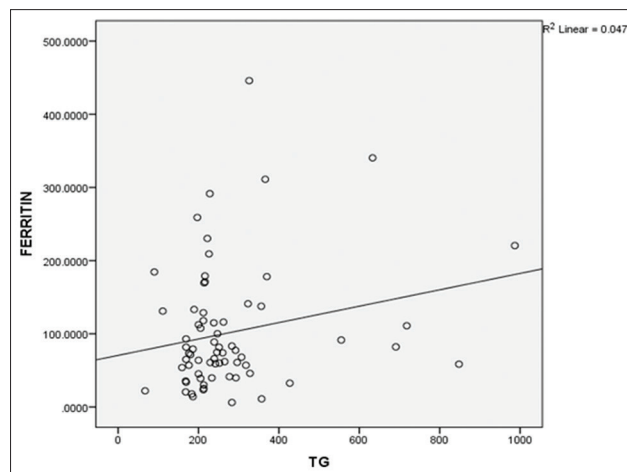
	r/P
Gp-1	0.307/0.010*
Gp-2	0.015/0.951

The study also found a statistically significant association between serum GGT and serum ferritin in the study group 1, the cases of MetS [Table 4].

The scatter plots derived for showing correlation of ferritin and GGT with different parameters in cases [Figures 1-6].

## Discussion

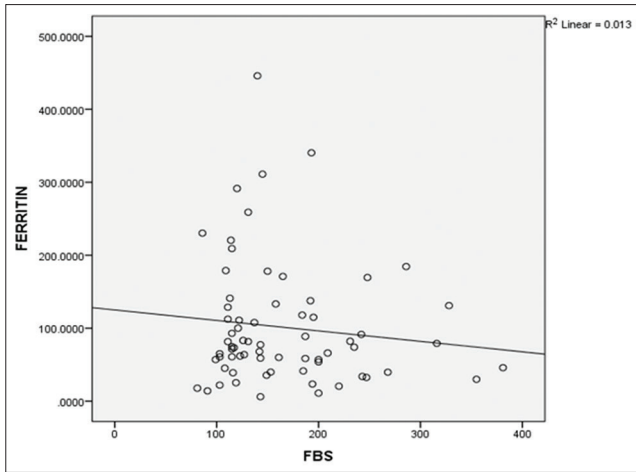
Metabolic syndrome is a state of chronic low-grade inflammation caused due to systemic oxidant stress induced by obesity and insulin resistance with increased activation of downstream signaling cascades that cause atherogenesis and tissue fibrosis.<sup>[15]</sup> A rise in inflammatory markers has been seen in MetS. Serum GGT and ferritin concentrations were significantly higher in subjects with metabolic syndrome compared to those without it. In subclinical inflammation, GGT could be elevated because of



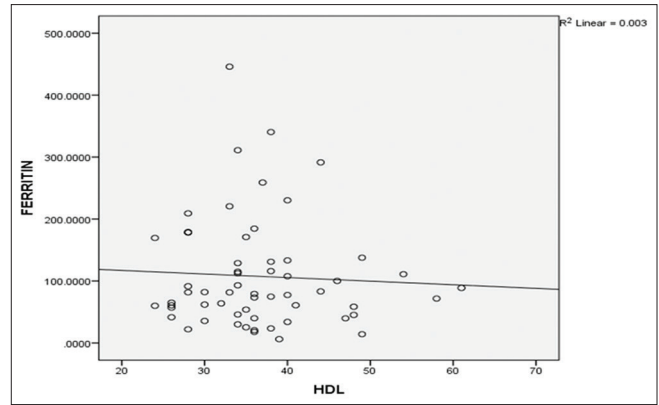
**Figure 1: Association between serum ferritin and serum TG in study group 1**

its role in glutathione homeostasis and oxidant stress.<sup>[16]</sup> Ferritin acts as an acute-phase reactant, and elevated serum ferritin levels might show systemic inflammation besides increased body iron stores. It has been observed that inflammation regulates the expression of ferritin mRNA and protein levels, and its secretion.<sup>[8]</sup> Excessive iron deposits produce hydroxyl radicals, which cause lipid peroxidation. Various studies have shown the same findings as the present study.<sup>[9,13,17]</sup> GGT showed a significant positive correlation with TG a defining parameter for MetS in cases also indicates the relationship between MetS and oxidant stress. Increased GGT levels lead to increased glutathione hydrolysis and causing more lipid peroxidation. Kaspagolu *et al.*<sup>[18]</sup> had the same finding. Shiraishi *et al.*<sup>[19]</sup> identified GGT as an important predictor for MetS. In this study, no significant correlation was seen between ferritin and any component of MetS. The possible reason could be a small sample size and the cross-sectional nature of the study. This was consistent with the research done by Ryu *et al.*<sup>[20]</sup> Serum GGT and ferritin were independently significantly correlated with each other.

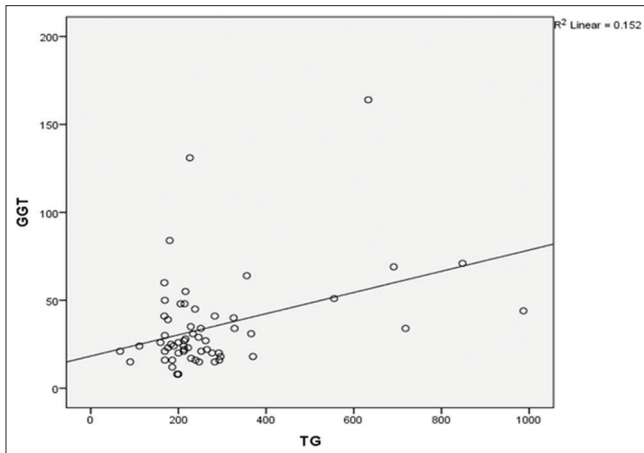
Wei D *et al.*<sup>[13]</sup>, in their research on the Chinese population, have also found a positive association. GGT is the principal enzyme that influences the extracellular hydrolysis of glutathione (GSH). Ferritin affects the catalytic activities of GGT. The reactive products generated from GGT-mediated



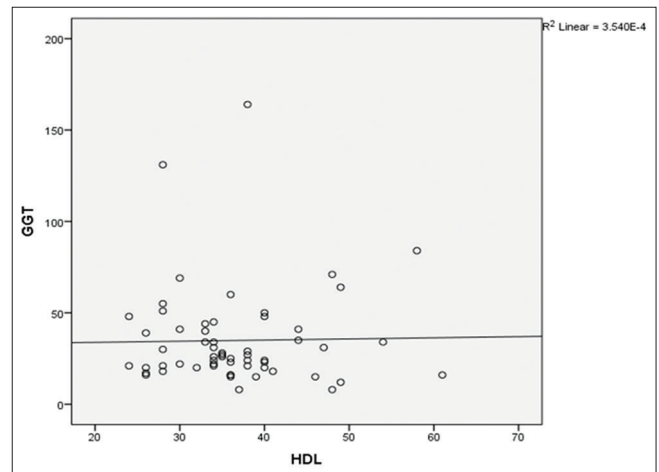
**Figure 2:** Association of serum ferritin with fasting blood sugar (FBS) in study group 1



**Figure 3:** Association of serum ferritin and serum HDL in study group 1



**Figure 4:** Association of serum GGT with serum TG in the study group 1



**Figure 5:** Association of serum GGT with serum HDL in study group 1

cleavage of GSH may cause the reduction of ferric iron to ferrous iron. Elevated levels of GGT and ferritin then result in increased production of reactive oxygen species (ROS), aggravating oxidative stress, and leading to peroxidation of lipids by highly reactive free radicals. The adverse effects of ferritin overload and increased GGT mutually reinforce each other, ultimately leading to tissue injury and increased risk of MetS and its consequences.

## Conclusion

Our study showed raised serum GGT and serum ferritin levels in cases of metabolic syndrome in comparison to control. The significant association of GGT with TG in MetS and between GGT and ferritin suggests their role towards increasing oxidant stress and inflammatory load in MetS, which is an inflammatory condition. This may further aggravate the risk of CVD. Further studies with a higher sample size and follow-up are required to reinforce these associations and will help in the utilization of

those findings in containing the risk of metabolic syndrome and its complications.

## Key Points

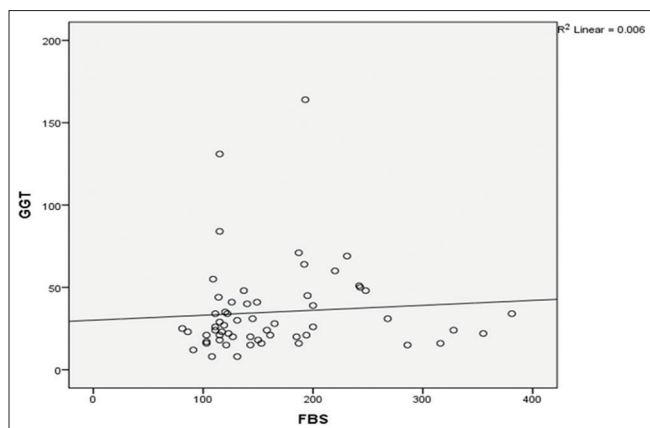
- Serum GGT and serum ferritin were significantly high in cases of MetS in comparison to the controls.
- A significant positive correlation of GGT with TG and waist circumference- diagnostic indices of MetS in cases.
- A significant association between GGT and ferritin in cases.
- Easy availability and relatively cheaper tests like GGT and ferritin can be used as a predictor for MetS in routine practice.

## Abbreviations

IFCC = International Federation Clinical Chemistry and Laboratory Medicine

LDL = Low density lipoprotein

CLIA = Chemiluminescence immunoassay



**Figure 6:** Association of serum GGT with serum FBS in study group 1

DM = Diabetes mellitus

GGT = Gamma glutamyl transferase

HTN = Hypertension

MetS = Metabolic Syndrome

NCEP/ATP = National Cholesterol Education Program/Adult Treatment Panel

ASCVD = Atherosclerotic cardiovascular disease

CAD = Coronary artery disease

CVD = Cardiovascular disease

TG = Triglycerides

HDL-C = High density lipoprotein- cholesterol

GOD-PAP (POD) = Glucose oxidase- peroxidase

MOD-IFCC = Modified IFCC

GPO-PAP = Glycerine phosphate oxidase peroxidase

### Ethical Clearance

Ethical clearance for the study was obtained by the Institute Ethics Committee. Certificate number: AIIMS RPR/IEC/2018/161.

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### Conflicts of interest

There are no conflicts of interest.

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