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# GGT as A Marker for Assessment of Metabolic Syndrome.

**Saba Nazneen Khan* and MV Kodliwadmath.**

Department of Biochemistry, Navodaya medical college, Raichur, Karnataka, India.

**ABSTRACT**

The Metabolic Syndrome is a constellation of metabolic abnormalities that confer increased risk of CVD and DM. Dominant risk factors for metabolic syndrome are central obesity and insulin resistance, exacerbating factors are physical inactivity, advancing age and genetic factors. To assess WC in metabolic syndrome patients and levels of FBG associated with dislipidemia. To correlate GGT with the components of metabolic syndrome. The study comprised of 50 cases with central obesity and 50 healthy controls. FBG, lipid profile, GGT were estimated. GGT was correlated with components of metabolic syndrome. In this study the WC (107.25± 3.62) was significantly high compared to control group (WC 71.8±8.5). A significant increase ($p>0.0001$) in lipid parameters and FBG were seen in cases as compared to controls. The levels of GGT (48.23± 23.92) were highly significant in cases as compared to controls. The present study showed that increased WC, FBG and dyslipidaemia are associated with increased GGT. Measuring waist circumference of patients could help in identifying abdominal adiposity which is being recognized as a useful measure for insulin resistance and MS. GGT was highly significantly correlated to the components of metabolic syndrome. Hence, it can be used as a predictive marker of metabolic syndrome and CVD risk assessment. Further longterm follow up studies are required to confirm the use of GGT as a marker of metabolic syndrome and CVD risk assessment.

**Keywords**: IDF – international diabetic federation, CVD –cardiovascular disease, GGT- gamma glutamyl transferase.

**Corresponding author*

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## INTRODUCTION

The Metabolic Syndrome (Syndrome X, Insulin Resistance Syndrome) consists of a constellation of metabolic abnormalities that confer increased risk of cardiovascular disease (CVD) and diabetes mellitus (DM).[1] It consists of an atherogenic dyslipidaemia (i.e., elevated triglycerides and apolipoprotein B (apo-B)) and low high density lipoprotein cholesterol (HDL-C), elevation of blood pressure and glucose, prothrombotic and proinflammatory states. The risk of ASCVD accompanying the MS is approximately doubled compared with an absence of the syndrome. The MS appears to promote the development of ASCVD at multiple levels. Elevations of apo-B containing lipoproteins initiate atherogenesis and drive lesion development. Atherosclerotic plaque development is accelerated by low levels of HDL-C, by elevated glucose levels and by inflammatory cytokines. Increasing frequency of abdominal obesity, reaching epidemic proportions, enhances the prevalence of metabolic syndrome. Both, obesity and metabolic syndrome have the potential to influence on the incidence and severity of cardiovascular disease with serious implications for worldwide health care systems.

Visceral obesity is a key component in the development of the metabolic syndrome. Increased central adiposity, particularly in visceral region, leads to greater free fatty acid flux and inhibition of insulin action. Adipose tissue in obesity is resistant to insulin which is associated with disturbed glucose metabolism in the muscles and liver. Even mild or moderate degree of obesity with concomitant insulin resistance may be associated with metabolic syndrome. On the other hand, excessive accumulation of abdominal fat may lead to the development of metabolic syndrome independently of the degree of insulin resistance [2]. MS is a complex web of metabolic factors that are associated with a 2-fold risk of CVD and a 5-fold risk of diabetes. Individuals with MS have a 30%–40% probability of developing diabetes and/or CVD within 20 years, depending on the number of components present [3]. Serum Gamma-Glutamyl Transferase (GGT) is an enzyme present on cell surfaces and in serum that contributes to the extracellular catabolism of glutathione (GSH), but most serum GGT is derived from the liver. Serum GGT is also a clinical marker of factors like: alcohol consumption & body fat content [4]. GGT has a pivotal role in the maintenance of intracellular defenses through its mediation of extracellular transport into most types of cells. Increased GGT may reflect not only hepatic oxidative stress (mediated by fat accumulation inside hepatocytes), but also systemic oxidative stress. Oxidative stress has been associated with insulin resistance in several studies. [5] The association between GGT and both MetS and type 2 diabetes incidence could reflect non-specific insulin resistance, associated with the oxidative stress process, whatever the organ localization, including hepatic insulin resistance. [6]

In this study we determine the parameters like waist circumference, lipid profile, blood glucose levels and GGT among patients of metabolic syndrome with central obesity and compared them with healthy individuals.

## MATERIALS AND METHODS

The present study comprised of 100 patients out of which 50 cases were with Metabolic Syndrome [Clinically diagnosed/confirmed cases of HTN and/ or DM/ glucose intolerance with central obesity (waist circumference ≥ 90cm (males), ≥ 80cm (female)] and 50 were healthy controls. The patients and healthy controls were between the age group of 20– 50 years. Study was conducted at Navodaya Medical College Hospital and Research Centre, Raichur from April 2013 to May 2014. Patients attending outpatient Department and those admitted were taken in the study. The patients and controls had voluntarily participated in the study. Patients with Juvenile and gestational diabetes, Smokers, Alcoholics, acute and chronic inflammatory and rheumatologic conditions /infectious disease were excluded from the study. In the present study Metabolic syndrome was defined using IDF consensus world wide definition [7].

### Collection of data

Every patient was evaluated by detailed history and clinical examination. Anthropometric measurement like waist circumference was measured. Overweight and obesity were defined by the age and sex specified cut off. Under aseptic precautions around 5mL of venous blood will be drawn. Serum is separated which will be used to estimate fasting blood glucose, lipid parameters and serum gamma glutamyl transferase immediately or within 2 hours when kept at 40 C. Parameters studied are :Fasting blood glucose (FBG) by Glucose oxidase -Peroxidase end point colorimetric method [8], Triglycerides by GPO Trinder method [9], Total

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cholesterol by CHOD-PAP method [10], HDL-C by phosphotungstic acid method end point [11], LDL-C and VLDL-C was calculated by Friedwald's equation [12], Gamma glutamyl transferase (GGT) by Szasz method [13].

**Statistical analysis**

The results for different profiles were expressed as mean ± SD. Comparison between control and case groups was done by student unpaired t – test. Pearson's correlation was applied to correlate between the parameters. A two – tailed P – value of less than 0.001 was considered significant. Data was analyzed using Microsoft excel, SPSS version 17.0 and Minitab version 14.0 software packages.

## RESULTS

**Table no: 1. Comparison of Age, BP, WC, Lipid profile and GGT between cases and controls.**

| VARIABLE | CASES (N=50) | | CONTROLS (N=50) | | T | P | Inference |
|---|---|---|---|---|---|---|---|
| | MEAN | SD | MEAN | SD | | | |
| Age (yrs) | 42.78 | 6.31 | 42.78 | 6.01 | 0.0001 | 1.0 (P>0.05) | N.S |
| SBP (mmHg) | 144.04 | 23.06 | 118.12 | 9.25 | 7.37 | 0.0001 (p<0.001) | H.S |
| DBP(mmHg) | 88.62 | 12.67 | 77.74 | 6.37 | 5.42 | 0.0001 (P<0.001) | H.S |
| WC (cms) | 107.25 | 10.46 | 71.8 | 8.5 | 18.58 | 0.0001 (P<0.001) | H.S |
| Blood glucose(mg/dL) | 129.59 | 30.67 | 83.96 | 11.58 | 9.84 | 0.0001 (P<0.001) | H.S |
| Serum Total Cholesterol (mg/dL) | 209.36 | 56.55 | 169.3 | 30.84 | 4.39 | 0.0001 (P<0.001) | H.S |
| Serum TG(mg/dL) | 191.20 | 87.63 | 108.01 | 25.95 | 6.43 | 0.0001 (P<0.001) | H.S |
| Serum HDL-Cholesterol(mg/dL) | 38.74 | 9.46 | 57.2 | 12.30 | 8.40 | 0.0001 (P<0.001) | H.S |
| Serum LDL-Cholesterol(mg/dL) | 132.79 | 59.35 | 90.65 | 30.52 | 4.46 | 0.0001 (P<0.001) | H.S |
| Serum VLDL-Cholesterol(mg/dL) | 38.07 | 17.50 | 23.12 | 12.78 | 4.91 | 0.0001 (P<0.001) | H.S |
| Serum GGT(U/L) | 48.23 | 23.92 | 23.47 | 9.81 | 6.77 | 0.0001 (P<0.001) | H.S |

**Table no: 2. Pearson's correlation of GGT with components of metabolic syndrome.**

| GGT vs. | WC | BP | | TG | HDL-C | FBG |
|---|---|---|---|---|---|---|
| | | SBP | DBP | | | |
| Pearson's correlation | 0.88 | 0.28 | 0.78 | 0.91 | -0.192 | 0.76 |
| p-VALUE | 0.032 (P<0.05) | 0.044 (P<0.05) | 0.045 (P<0.05) | 0.02 (P<0.05) | 0.018 (P<0.05) | 0.035 (P<0.05) |
| N | 50 | 50 | 50 | 50 | 50 | 50 |
| Inference | Significant | Significant | Significant | Significant | Significant | Significant |

Table no.1: The difference of systolic BP and diastolic BP of cases were statistically highly significant (p< 0.001) as compared to controls. But difference in mean± SD of age of cases was not significant (p>0.05) as compared to controls. Table no. 1: shows the difference of mean±SD of age in cases and controls were 42.78±6.31 and 42.78±6.01 respectively. The difference of mean± SD of systolic BP in cases and controls were 144.04 ± 23.06 and 118.12±9.25 respectively, the difference of mean ± SD of diastolic BP in cases and controls were 88.6±12.67 and 77.74±6.37 respectively. Statistically there was highly significant increase (p<0.001) in waist circumference, FBG, lipid parameters (except HDL-C) and GGT of cases as compared to controls. Table no: 1. shows the mean ± SD of waist circumference in cases and controls were 107.25± 10.46 and 71.8± 8.5 respectively, mean ± SD of fasting blood glucose in cases and controls were 129.59± 30.67 and 83.96± 11.58 respectively, the mean ± SD of serum total cholesterol in cases and controls were 209.36 ± 56.55 and 169±

30.84 respectively, the mean ± SD of serum TG in cases and controls were 191.20 ±87.63 and 108.01± 25.95 respectively, the mean ± SD of serum HDL- Cholesterol in cases and controls were 38.74 ± 9.46 and 57.2± 12.30 respectively, the mean ± SD of serum LDL- Cholesterol in cases and controls were 132.79 ± 59.35 and 90.65 ± 30.52 respectively, the mean ± SD of serum VLDL-Cholesterol in cases and controls were 38.07 ± 17.50 and 23.12± 12.78 respectively and the mean ± SD of serum GGT in cases and controls were 48.23 ± 23.92 and 23.47± 9.81 respectively.

Table no: 2. shows Pearson's correlation between serum GGT and components of metabolic syndrome in the cases. It is evident from the table that serum GGT has positive correlation with WC, BP, serum TG and FBG and a significant negative correlation with HDL-C. Hence it is interpreted that serum GGT is strongly associated with the components of metabolic syndrome.

**DISCUSSION**

Waist circumference is a good index in assessing of central obesity and also a good predictor tool of insulin resistance. The present study has used IDF criteria for waist circumference that is more applicable to Asian Indian population and shows that there was statistically significant increase in waist circumference of cases as compared to healthy controls. Waist circumference when assessed independently is more predictive of metabolic syndrome compared to other anthropometric measures like BMI and WHR. Although neither BMI nor waist circumference provides a complete picture of overall risk. Waist circumference of the subjects from present study revealed stronger association with other multiple components of metabolic syndrome. In 2003, Ramachandran et al. [14] conducted a study among urban Asian Indian adults to determine the prevalence of metabolic syndrome and in 2005 Dong Feg Gu et al.[4] conducted a study to know the prevalence of metabolic syndrome among overweight adults in China, these studies showed similar values of waist circumference as compared to present study. In the year 2010 Ghazali S. M. and Sanusi R. A. [15] showed in their study, among those diagnosed with MS, WC was found to have statistically significant positive correlation with FPG and TG being higher than those of WHR and BMI in the NCEP-ATP III category. While WC shows strong positive but not statistically significant correlation with DBP, SBP and FPG being higher than those for BMI and WHR in the WHO category. Hypertension is a very common condition which frequently remains undiagnosed until relatively late in its course leading to a variety of other life threatening conditions like heart failure. It is a very prominent feature of MS, present in upto 85% of patients. In the year 2006, Kelminda Bulhoes and Leila [16] conducted a study among all hypertensive patients to study the prevalence of metabolic syndrome in hypertensive patients and showed that the most frequent combination was arterial hypertension and increased waist circumference followed by low HDL- Cholesterol which is the factor of metabolic syndrome most associated with hypertension. In 2007 Anil Nigam et al. [17] conducted a study to identify the contributions of fasting and postprandial glycemia to cardiovascular risk and has shown that IFG is associated with 1.2 fold increase in both all cause and cardiovascular morbidity and diabetes was associated with 1.51 fold increased risk of CV mortality and present study shows highly significant increase in FBG of cases as compared to controls. The characteristic dyslipidaemia in metabolic syndrome is elevation of serum TG and decrease in HDL-Cholesterol levels. However, in present study at least one lipid abnormality is present in >95% of cases. HDL-Cholesterol is antiatherogenic (enhances reversed cholesterol transport, anti inflammatory property and ability to protect LDL modification). Obesity itself reduces HDL-Cholesterol levels and the obese patients with metabolic syndrome and atherogenic dyslipidaemia almost always have reduced HDL-Cholesterol. In the year 2011, Ryuichi Kawamoto et al. [4] conducted a study to demonstrate association between lipid profiles and metabolic syndrome variables, showing that TG was significantly strongly associated with all three MetS-associated variables in both men and women and concluded that lipid ratios of TG/HDL-C, T-C/HDL-C, LDL-C/HDL-C as well as TG and HDL-C were consistently associated with MetS, insulin resistance and serum HMW Adiponectin. Lipid ratios may be used as reliable markers.

Increase in GGT is considered as predictor of CVD. Our study shows values of GGT are significantly higher than compared to B Kasapoglu et al [18]. B Kasapoglu et al shows that GGT may play a role in early diagnosis of metabolic syndrome with a high predictive value for both metabolic syndrome and cardiovascular disease. Excess of fat in the liver could enhance the oxidative stress, leading to overconsumption of GSH with a compensatory increase in GGT synthesis. The study conducted by Taki et al. [19] shows statistical increase in ALT, AST and GGT in metabolic syndrome group as compared to non – metabolic syndrome group. GGT was remarkably high with more than two fold increases in subjects with metabolic syndrome when compared to non- metS subjects. There was remarkable impact of waist circumference on GGT levels, with the large waist

circumference showing significantly higher GGT than the normal waist group. It may be interpretive from the findings of this study that patients due to obesity are at an earlier stage of pathogenesis of diabetes and GGT activity could be considered as a marker of whole body insulin sensitivity. The reasons for this hypothesis could be attributed, firstly to the explanation that GGT may relate to diabetes as it is a marker of oxidative stress. GGT has a pivotal role in the maintenance of intracellular defenses through its mediation of extracellular transport into most types of cells. Increased GGT may reflect not only hepatic oxidative stress (mediated by fat accumulation inside hepatocytes), but also systemic oxidative stress. Oxidative stress has been associated with insulin resistance in several studies [5]. The association between GGT and both MetS and type 2 diabetes incidence could reflect non-specific insulin resistance, associated with the oxidative stress process, whatever the organ localization, including hepatic insulin resistance [6].

Secondly, GGT might be interpretated as a marker for hepatic steatosis and hepatic IR in the pathogenesis of type 2 diabetes. Elevated GGT is strongly associated with obesity and excess deposition of fat in the liver termed NAFLD, which is thought to cause hepatic insulin resistance and to contribute to the development of systemic insulin resistance and hyperinsulinemia. Insulin resistance is the main pathogenic factor in the etiology of NAFLD in adults [20] and children. [21] Because fatty liver has been linked to insulin resistance syndrome/or type 2 diabetes, GGT could serve as a marker of the IR syndrome in the pathogenesis of diabetes.

Thirdly, serum GGT activity probably reflects chronic inflammation associated with low levels of anti inflammatory hormones present in obesity e.g. adinopectin or with reduced effectiveness of insulin as a modulator of cytokine action [22]. Obesity is associated with an increased number and/or size of adipose tissue cells. The cells overproduce hormones such as leptin and resistin and cytokines, such as tumor necrosis factor alpha (TNFα), some of which appear to cause cellular resistance to insulin by interfering with autophosphorylation of the insulin

The Reference range of GGT is < 32U/L for females and <55U/L for males, these cutoff values are used as a marker for hepatobiliary disorder. There is a need to establish cutoff values to be used as a marker of metabolic syndrome and CVD risk. This observed correlation indicates that monitoring of GGT along with WC, FBG, TG, HDL-C and BP in obese individuals can prevent the development of metabolic syndrome and CVD risk. GGT could be used as a predictive marker of metabolic syndrome and CVD risk. Further longterm follow up studies are required to confirm the use of GGT as a marker of metabolic syndrome and CVD risk.

## CONCLUSION

Measuring waist circumference of patients could help in identifying abdominal adiposity which is being recognized as a useful measure for insulin resistance and CVD risk. GGT was highly significantly correlated to the components of metabolic syndrome and is the marker of body fat content and oxidative stress. It may be concluded from our study that monitoring GGT along with WC, FBG, TG, HDL-C and BP in obese individuals can prevent the development of metabolic syndrome and CVD risk. Hence, it can be used as a predictive marker of metabolic syndrome and CVD risk assessment. Further longterm follow up studies are required to confirm the use of GGT as a marker of metabolic syndrome and CVD risk assessment.

The message emerging from this study is how best to define and screen for metabolic syndrome, considering energy stores on the one hand and health risks on the other. Our study is consistent with the saying “thinking about heart, then look at your waist”.

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