



Journal of Medical Sciences

ISSN 1682-4474

science
alert

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JMS (ISSN 1682-4474) is an International, peer-reviewed scientific journal that publishes original article in experimental & clinical medicine and related disciplines such as molecular biology, biochemistry, genetics, biophysics, bio-and medical technology. JMS is issued eight times per year on paper and in electronic format.

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Gamma-glutamyl Transferase in Diabetic Individuals with the Metabolic Syndrome in Calabar, Nigeria

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Increased Gamma-glutamyl Transferase (GGT) levels have been associated with diabetes and the metabolic syndrome. Our objective was to determine if GGT levels are significantly increased in diabetic patients with the metabolic syndrome and its relationship with cardiovascular risk factors in this group of patients. This study estimated GGT, glucose, triglycerides and high density lipoprotein cholesterol (HDL-C) levels in 60 diabetic outpatients of the University of Calabar Teaching Hospital (UCTH) and 34 age matched controls using kinetic colorimetric method for GGT and enzymatic colorimetric method for the others. Thirty nine of the diabetic subjects were diagnosed with metabolic syndrome using the World Health Organization (WHO) criteria for the diagnosis of metabolic syndrome. The mean body mass index, waist-hip ratio, systolic and diastolic blood pressure, Glucose, Triglycerides (TG) and Atherogenic Index of Plasma (AIP) levels of the diabetic subjects were significantly higher ($p < 0.05$) than those of the control group. The mean BMI, waist-hip ratio, systolic and diastolic blood pressure, glucose, TG, GGT and AIP levels were significantly higher ($p < 0.05$) in diabetics with the metabolic syndrome than controls. They also had a significantly higher ($p < 0.05$) systolic and diastolic blood pressure, TG and AIP level than normotensive diabetics without the metabolic syndrome. Normotensive diabetics without the metabolic syndrome had a significantly higher ($p < 0.05$) waist-hip ratio, systolic blood pressure and glucose levels when compared to controls. Gamma-glutamyl Transferase (GGT) levels were raised in diabetics with the metabolic syndrome and could be a marker for increased cardiovascular risk.

Key words: Gamma glutamyl transferase, diabetes, metabolic syndrome

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INTRODUCTION

The metabolic syndrome is a cluster of the most dangerous heart attack risk factors: diabetes and prediabetes, abdominal obesity, high cholesterol and high blood pressure (IDF, 2006). It is estimated that around 20-25% of the world population have this syndrome (Dunstan *et al.*, 2002) and they are three times as likely to have and twice as likely to die from a stroke or heart attack compared with people without the syndrome (Isomaa *et al.*, 2001).

Research evidence have found That Gamma-glutamyl Transferase (GGT) which is found in the liver, kidney, pancreas, epididymis, fibroblasts, lymphocytes and lung, adsorbs onto circulating Low Density Lipoprotein (LDL) and can catalyze their oxidation, a step necessary for the formation of foam cells and atherosclerotic plaques (Paolicchi *et al.*, 2006). Other evidence shows that it is expressed in the atheromatous core of coronary plaques where it co-localizes with oxidized LDL and foam cells (Paolicchi *et al.*, 2004). Gamma-glutamyl transferase may also have proinflammatory properties, because it mediates the interconversion of glutathione-containing inflammatory mediator leukotriene C4 into leukotriene D4 (Anderson *et al.*, 1982). This becomes important as inflammatory mechanisms mediate initiation, progression and the complications of atherosclerotic lesions (Libby *et al.*, 2002).

As atherosclerosis have been found to increase CVD risk which results in about half of all deaths and serious morbidity in urbanized communities especially the western world (Scheon, 2004), and as most African societies are tending towards western habits and diet, it is pertinent to determine serum concentrations of GGT in individuals with metabolic syndrome in an African locality to ascertain if there is any association between GGT levels and the metabolic syndrome as other experimental evidence suggests.

MATERIALS AND METHODS

A total of 94 subjects were used in the study. Sixty were diabetic outpatients on routine check-up at the University of Calabar Teaching Hospital (UCTH) in Calabar, Cross River State. Thirty nine of the 60 diabetic outpatients were diagnosed with the metabolic syndrome after experimental evidence in relation to the World Health Organization criteria for the diagnosis of metabolic syndrome (WHO, 1999). Most of the above subjects were on treatment for various components of the metabolic syndrome. The other 34 subjects were made up of apparently healthy individuals who have been excluded from having the metabolic syndrome by the same criteria

used above. This latter group of subjects were the control subjects and all 94 subjects were made up of males and females between the age of 30 and 75 years. Informed consent was obtained from the participants.

After explanation of the project objective to the subjects, a questionnaire was used to obtain the medical and therapeutic history of the subjects as well as demographic data. The blood pressure was measured using a mercury sphygmomanometer after subjects have rested for at least 5 minutes in a sitting position. The Body Mass Index (BMI) and waist-hip ratio were also obtained after necessary measurements and blood samples were taken after an overnight fast (between 10-12 hours), typically between 7 a.m. and 9 a.m. Blood was immediately centrifuged, and plasma and serum specimens were stored at -20°C until assayed. Plasma glucose was estimated by enzymatic (GOD-PAP) colorimetric method (Trinder, 1969). Serum HDL-C estimation was performed by precipitation of the non-HDL-C by the dextran sulphate-Mg (II) precipitation method and subsequent determination of HDL-C in the supernatant using CHOD-PAP enzymatic colorimetric method (Albers *et al.*, 1978 ; Allain *et al.*, 1974). Triglyceride was estimated using the GPO- PAP enzymatic colorimetric method (Schettler and Nussel, 1975). GGT activity in serum was performed using the kinetic colorimetric method (Persijn and van der Slik, 1976).

Student t-test was used to ascertain if there was a significant difference between the mean values of parameters obtained from all diabetic subjects and the controls. One way analysis of variance (ANOVA) was used to ascertain if a significant difference exist in the mean values of parameters obtained from diabetics with the metabolic syndrome, normotensive diabetics without the metabolic syndrome, hypertensive diabetics without the metabolic syndrome, and control group. Pairwise comparison of the ANOVA results was done using the Least Significant Difference (LSD) test. Pearson correlation analysis was also carried out.

RESULTS

Table 1 shows the age, Body Mass Index (BMI), waist-hip ratio, systolic and diastolic blood pressure of all diabetic subjects and controls. The mean BMI, waist-hip ratio, systolic and diastolic blood pressure in diabetics were significantly higher ($p < 0.05$) than those of the control subjects while there was no significant difference ($p > 0.05$) between the ages of the diabetic and control subjects.

Table 2 shows as stated in the title, the measured biochemical parameters of all diabetic subjects and

Table 1: Comparison of physical parameters of diabetic subjects with controls

Parameters					
Subjects	Age (years)	BMI (kg m ⁻²)	Waist hip ratio	SBP (mmHg)	DBP (mmHg)
Diabetics (n = 60)	53.07±9.90	27.65±5.13	0.90±0.05	138.17±19.59	86.92±12.25
Control (n = 34)	49.32±8.97	24.67±3.01	0.86±0.02	112.94±10.23	77.00±5.87
p-value t-test	p>0.05	p<0.05	p<0.05	p<0.05	p<0.05
Remark	NS	S	S	S	S

Mean±SD, NS: Not significant, S: Significant, SBP: Systolic blood pressure, DBP: Diastolic blood pressure

Table 2: Comparison of some biochemical parameters of diabetic subjects with controls

Parameters					
Subjects	Glucose (mmol L ⁻¹)	TG (mmol L ⁻¹)	HDL-C (mmol L ⁻¹)	GGT (U L ⁻¹)	AIP
Diabetics (n = 60)	7.61±2.97	1.35±0.36	1.18±0.24	130.25±40.53	0.05±0.18
Control (n = 34)	4.11±0.56	1.09±0.25	1.25±0.20	109.62±33.47	-0.06±0.14
p-value t-test	p<0.05	p<0.05	p>0.05	p<0.05	p<0.05
Remark	S	S	NS	S	S

Mean±SD, NS: Not significant, S: Significant

Table 3: Physical parameters of diabetics with the metabolic syndrome, normotensive diabetics without the metabolic syndrome, hypertensive diabetics without the metabolic syndrome and controls

Parameters				
Subjects	BMI (kgm ⁻²)	Waist-hip ratio	SBP (mmHg)	DBP (mmHg)
Diabetics with metabolic syndrome (n = 39)	28.26±5.32*	0.91±0.05*	143.46±20.68**	90.26±11.97**
Normotensive diabetics without metabolic syndrome (n = 16)	27.23±4.93	0.89±0.05*	124.68±11.26*	77.19±8.36
Hypertensive diabetics without metabolic syndrome (n = 5)	24.26±3.05	0.86±0.03	140.00±9.35*	92.00±8.37**
Control (n = 34)	24.67±3.01	0.86±0.06	112.94±10.23	77.00±5.87
ANOVA p-value	p<0.05	p<0.05	p<0.05	p<0.05
Remark	S	S	S	S

Mean±SD, S: Significant, *Significantly higher than control (p<0.05), **Significantly higher than normotensive diabetics without the metabolic syndrome (p<0.05)

controls. They included mean glucose, Triglyceride (TG), High Density Lipoprotein Cholesterol (HDL-C), Gamma-glutamyl Transferase (GGT) and Atherogenic Index of Plasma (AIP) levels. The mean glucose, TG, GGT and AIP levels in diabetics were significantly higher (p<0.05) than those of controls while there was no significant difference (p>0.05) between the HDL-C levels of the diabetic and control subjects.

Table 3 shows the physical parameters of diabetic subjects with the metabolic syndrome, normotensive diabetics without the metabolic syndrome, hypertensive diabetics without the metabolic syndrome and controls. There was a significant difference (p<0.05) in the mean values of the BMI, waist-hip ratio, systolic and diastolic blood pressure of the different groups above and controls. Pair-wise comparison of the mean values of parameters of the various groups showed that mean values of BMI, waist-hip ratio, systolic and diastolic blood pressure were significantly higher (p<0.05) in diabetics with the metabolic syndrome than those of controls. Normotensive diabetics without the metabolic syndrome had a significantly higher (p<0.05) waist-hip ratio and systolic blood pressure than the control group. Hypertensive diabetics without the metabolic syndrome

had only their systolic and diastolic blood pressure significantly higher (p<0.05) than those of the control group. Diabetics with the metabolic syndrome had a significantly higher (p<0.05) systolic and diastolic blood pressure than those of normotensive diabetics without the metabolic syndrome and hypertensive diabetics without the metabolic syndrome had only their diastolic blood pressure significantly higher (p<0.05) than those of normotensive diabetics without the metabolic syndrome.

Table 4 shows the biochemical parameters measured in diabetic subjects with the metabolic syndrome, normotensive diabetics without the metabolic syndrome, hypertensive diabetics without the metabolic syndrome and controls. There was a significant difference (p<0.05) in the mean levels of glucose, TG, GGT and AIP and no significant difference (p>0.05) in the mean HDL-C levels of the different groups above and controls. Pair-wise comparison of the mean values of parameters of the various groups showed that diabetics with the metabolic syndrome had a significantly higher (p<0.05) glucose, TG, GGT and AIP levels when compared to the control group. They also have a significantly higher (p<0.05) TG and AIP level when compared to normotensive diabetics without the metabolic syndrome. Both normotensive and

Table 4: Some biochemical parameters of diabetics with the metabolic syndrome, normotensive diabetics without the metabolic syndrome, hypertensive diabetics without the metabolic syndrome and controls

Subjects	Parameters				
	Glucose (mmol L ⁻¹)	TG (mmol L ⁻¹)	HDL-C (mmol L ⁻¹)	GGT (U L ⁻¹)	AIP
Diabetics with metabolic syndrome (n = 39)	7.52±3.03*	1.41±0.39**	1.15±0.26	134.51±40.52*	0.08±0.18**
Normotensive diabetics without metabolic syndrome (n = 16)	7.18±2.94*	1.18±0.27	1.25±0.18	116.88±43.30	-0.03±0.16
Hypertensive diabetics without metabolic syndrome (n = 5)	9.62±2.02**	1.39±0.22	1.10±0.17	139.80±24.37	0.10±0.11*
Control (n = 34)	4.11±0.56	1.09±0.25	1.25±0.20	109.62±33.47	-0.06±0.14
ANOVA					
p-value	p<0.05	p<0.05	p>0.05	p<0.05	p<0.05
Remark	S	S	NS	S	S

Mean±SD, S: Significant, NS: Not Significant, *Significantly higher than control (p<0.05), **Significantly higher than normotensive diabetics without the metabolic syndrome (p<0.05)

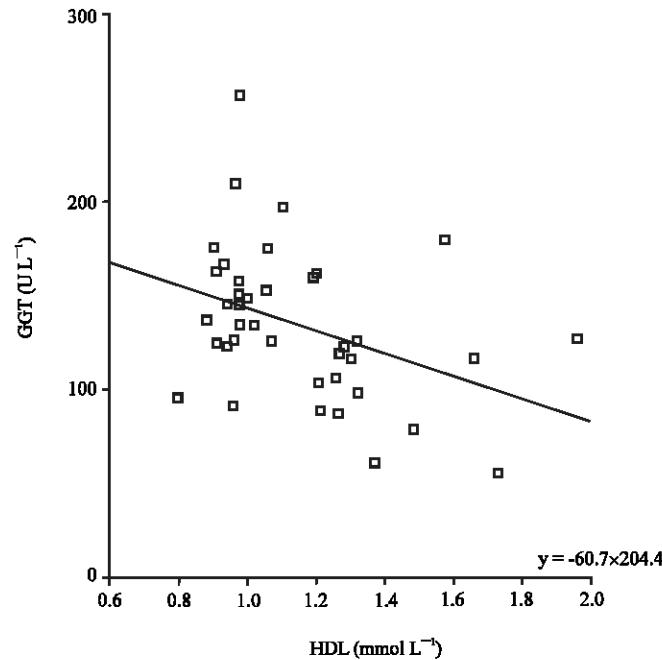


Fig. 1: Correlation graph of gamma-glutamyl transferase (GGT) against high density lipoprotein cholesterol (HDL-C) in subjects with metabolic syndrome

hypertensive diabetics without the metabolic syndrome had a significantly higher (p<0.05) glucose level when compared to the control group. Hypertensive diabetics without the metabolic syndrome had a significantly higher (p<0.05) glucose level than those of normotensive diabetics without the metabolic syndrome. They also have a significantly higher (p>0.05) AIP level when compared to controls.

Correlation analysis carried out showed that there was a negative correlation between GGT and HDL-C (r = -0.39, p<0.05) in diabetic subjects with the metabolic syndrome (Fig. 1 and 2). shows a negative correlation between TG and HDL-C (r = -0.48, p<0.05) in diabetics with the metabolic syndrome.

DISCUSSION

In the present study glucose levels were significantly higher in diabetics when compared to controls. Both diabetics with the metabolic syndrome and those without the syndrome showed higher glucose levels than controls. The raised glucose levels were expected because diabetics have a relative insulin deficiency or insulin resistance and in some cases both (IDF, 2006). Insulin resistance has also been reported by many workers to play an important role in the etiology of the metabolic syndrome (Hu *et al.*, 2004; IDF, 2006). The presence of insulin resistance and/or deficiency leads to impairment of glucose entry into cells leading to hyperglycaemia. Thus cells cannot produce enough ATP

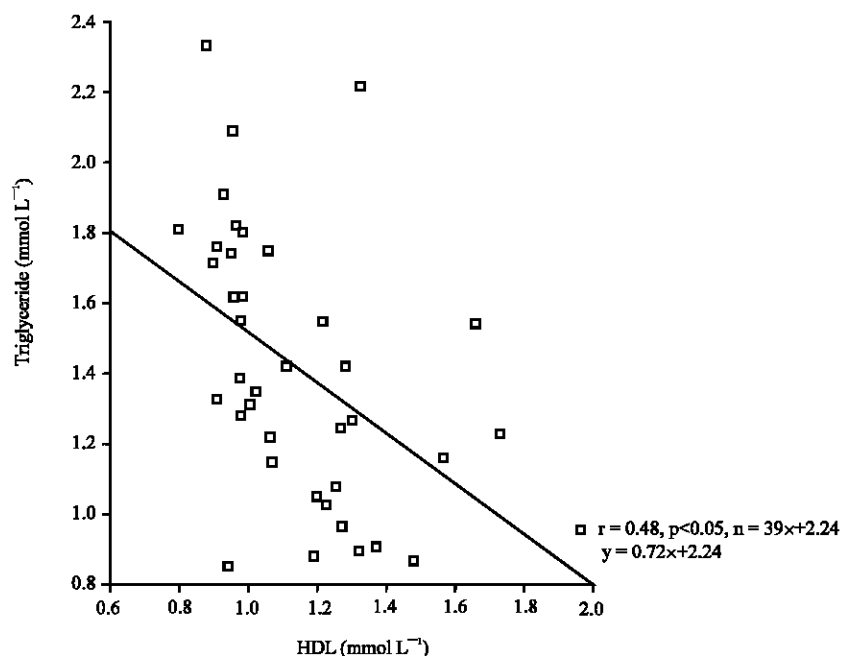


Fig. 2: Correlation graph of triglyceride against high density lipoprotein cholesterol (HDL-C) in subjects with metabolic syndrome

(Adenosine Triphosphate) due to lack of intracellular glucose and this leads to activation of gluconeogenic mechanisms to produce more glucose which aggravates the hyperglycaemia. Most of the diabetic subjects were on drug therapy to control glucose levels and this is the reason why their glucose levels were not excessively increased above the upper limit of normal. Hypertensive diabetics without the metabolic syndrome had a significantly higher glucose level than normotensive diabetics without the metabolic syndrome and this may be due to differences in response to treatment though there are no clear mechanisms to support this finding.

Normal levels of insulin and insulin sensitivity inhibits lipolysis but when insulin is deficient or insulin resistance is present, lipolysis is accelerated and plasma Non-esterified Fatty Acids (NEFA) concentrations rise (Crook, 2006). This is re-esterified to form TG in the liver and incorporated into Very Low Density Lipoprotein (VLDL). The accumulation of VLDL in plasma result in increased serum triglycerides as the enzyme lipoprotein lipase which is necessary for the catabolism of VLDL requires insulin for optimal activity. The raised TG levels in diabetics indicates that the above mechanisms are in play and as above, treatment may have slowed down this process so that TG levels are not excessively increased above the upper limit of normal.

Both Body Mass Index (BMI) and waist-hip ratio are measures of body fat and its distribution. Though the mechanism by which excessive fat cause insulin

resistance and impairs glucose metabolism is not clearly defined (IDF, 2006), fat stores (especially visceral fat) are an important cause of increased NEFA and TG in skeletal muscles which impairs insulin secretion (Ginsberg and Stalenhoef, 2003). Both BMI and waist-hip ratio were significantly increased in diabetics with the metabolic syndrome when compared to controls and this may account for the significantly higher TG levels seen only in this group. Normotensive diabetics without the metabolic syndrome had a significantly higher waist-hip ratio than controls but not BMI and this may not have been enough to cause a significant increase in TG when compared to controls. These findings suggest that the presence of increased BMI and waist-hip ratio may synergistically produce more risk factors for Cardiovascular Disease (CVD). Visceral fat also secrete adipokines like resistin and tumour necrosis factor alpha (TNF- α) that increase insulin resistance. The effect of increased fat on glucose concentrations may have been masked by drug therapy.

High Density Lipoprotein Cholesterol (HDL-C) levels in all diabetics and the different diabetic groups were not significantly different from controls. Other workers (Alberti and Zimmet, 1998; Sheetz and King, 2002; Grundy *et al.*, 2004) reported that low HDL-C levels are associated with the metabolic syndrome and diabetes. In hypertriglyceridaemia, HDL becomes overloaded with triglyceride under the action of hepatic lipase. This causes a reduction in their size and also, they loose apo A-1 resulting in a fall in their concentration (Crook, 2006). The

slightly raised TG levels of all diabetics and the different diabetic groups probably due to therapy may not have been enough to elicit the above processes resulting in no significant fall in HDL-C concentrations.

Since Gaziano *et al.* (1997) reported that the ratio of triglycerides to HDL was a strong predictor of myocardial infarction, other findings supporting this claim have been made. Dobiaova (2004) showed that Atherogenic Index of Plasma (AIP) calculated by the formula; $\log(TG/HDL-C)$ may reflect delicate changes in the lipoprotein fractions. Findings from this study using this index showed that diabetics have increased cardiovascular risk when compared to controls. It was interesting to find that AIP was higher in diabetics with the metabolic syndrome and hypertensive diabetics without the syndrome when compared to controls and that it was also higher in diabetics with the metabolic syndrome when compared to normotensive diabetics without the syndrome. This finding suggests that cardiovascular risk increases with increase in components of the metabolic syndrome as reported by other workers such as Hu *et al.* (2004).

Raised blood pressure has been associated with insulin resistance (Sowers and Frohlich, 2004) and most of the diabetic subjects had hypertension. Though mechanisms are unclear, insulin resistance and hyperglycaemia may contribute to increased blood pressure but the cause of increased blood pressure in most diabetics is probably multifactorial.

Gamma-glutamyl Transferase (GGT) levels were raised in diabetics. Only diabetics with the metabolic syndrome had a significantly higher GGT levels than controls. Other workers have also observed elevated GGT levels in diabetics and individuals with the metabolic syndrome (Rantala *et al.*, 2000; Colantes *et al.*, 2006). The mechanisms involved in the increase of GGT levels in these individuals remain unclear although several mechanisms have been suggested. Krefetz and McMillin (2005) suggested that the source of GGT increase in diabetes is probably from the pancreas. Others believe that hepatic steatosis which is common in diabetes and the metabolic syndrome may be the result of GGT increase in these individuals either due to low grade hepatic inflammation or hepatocellular damage leading to GGT stimulation (Ortega *et al.*, 2006). Alternatively, fat in the liver could enhance oxidative stress leading to glutathione consumption and hence stimulation of GGT (Grundy, 2007). Though some workers like Emdin *et al.* (2005) proposed that GGT may be proatherogenic, a direct role in causation of atherosclerosis is yet to be determined. The raised GGT levels in diabetics with the metabolic syndrome suggest that mechanisms that may result in its increase are in play and that these mechanisms were not

rapid enough in normotensive and hypertensive diabetics without the metabolic syndrome to result in their increase. This finding agrees with the report of other workers that increased GGT is linked with the metabolic syndrome and could be a marker for its presence.

Gamma-glutamyl transferase correlated negatively with HDL-C in diabetics with the metabolic syndrome which was contrary to the findings of Rantala *et al.* (2000) who observed a positive correlation of GGT with HDL-C in hypertensive individuals with the metabolic syndrome, most of whom consumed alcohol. The strong increasing effect of alcohol on GGT and also HDL-C may have obscured this relationship in the other studies as most of the subjects with metabolic syndrome in the present study reported abstinence from alcohol. Underlying mechanisms to this finding is unclear and as low HDL-C levels are an independent predictor of cardiovascular disease, this relationship suggests that increased GGT may be a marker of increased risk of cardiovascular disease.

The negative correlation between TG and HDL-C support reports of Robins *et al.* (2003) and Grundy *et al.* (2004) who also observed this in their study. It indicates presence of atherogenic dyslipidaemia which is commonly denoted by the presence of increased TG and low HDL-C. As discussed above, hypertriglyceridaemia leads to the overloading of HDL-C with TG under the action of hepatic lipase and this leads to the loss of apo A1 and also a reduction in their size, and hence their concentration falls. The negative correlation between TG and HDL-C in diabetics with the metabolic syndrome suggests that the above processes are ongoing and was not overtly evident probably due to therapy.

CONCLUSION

From this study, it is concluded that there is increased risk of cardiovascular disease in diabetic individuals and this risk is enhanced by the metabolic syndrome and its components. Elevated levels of GGT in individuals may not always indicate consumption of alcohol or hepatobiliary disease but may suggest the presence of diabetes and the metabolic syndrome as elevated GGT levels is linked to these conditions.

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