LASU Journal of Medical Sciences
Official Publication of the Faculty of Basic Medical Sciences
Lagos State University College of Medicine, Ikeja
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Research Articles

Plasma Lipoprotein Lipase Activity and Dyslipidaemia among Type 2 Diabetic Patients

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Keywords:
Diabetes Mellitus, Hypertriglyceridemia, Lipoprotein Lipase activity, Dyslipidaemia, Total cholesterol, Glycated Hemoglobin

SUMMARY

Objectives: Lipoprotein Lipase activity has been proven to be decreased in type 2 diabetes mellitus (DM) causing hypertriglyceridemia and elevated low density lipoprotein cholesterol (LDL-C). The interplay of these deranged lipids plays an important role in the pathogenesis of cardiovascular diseases. This study was designed to assess for the relationship between plasma lipoprotein lipase activity and dyslipidaemia in type 2 diabetes.

Method: This is a descriptive cross-sectional study conducted between January and March 2017. A total of 166 type 2 DM participants and 166 apparently healthy and age–matched controls were included in the study. Lipoprotein lipase activity, glycated haemoglobin (HbA1c), plasma total cholesterol (TC), triglycerides (TG), low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C) were analysed in the subjects and control group. Results from laboratory analysis and other data were subjected to statistical analysis using SPSS version 20.

Results: Diabetics had significant (p value ≤0.01) elevations of plasma TC of 185.7±45.1, LDL-C of 142.0±43.5 and HbA1c level of 8.30±2.4 compared to the controls. The lipoprotein lipase activity of 57.3±3.7 was significantly lower when compared with the control group. There was an inverse relationship between plasma lipoprotein lipase activity, TC and LDL-C in type 2 diabetes.

Conclusion: These findings may suggest that type 2 DM is associated with reduced activity of lipoprotein lipase enzyme which plays an important role in lipid metabolism and dyslipidaemia with an increased risk of cardiovascular diseases.

INTRODUCTION

Diabetes Mellitus (DM) is a diverse group of metabolic disorders that is often associated with a high morbidity, mortality and an economic burden in Nigeria.[1] Diabetes Mellitus has been classified as insulin-dependent (Type 1) in which there is impaired insulin secretion and Non-insulin dependent (Type 2) in which there is resistance to the action of insulin.

Type 2 diabetes is increasingly becoming a major chronic disease with about 14 million individuals estimated to have DM in Africa, and a projected estimate of 28 million by 2030.[2] Urbanization with changing patterns of diet, physical inactivity, and ageing populations are the major drivers of this increasing prevalence of diabetes in Africa.[2]

Diabetes Mellitus has also been described as a cause of several other important and often lethal non-communicable diseases such as cardiovascular and renal diseases which have considerable impacts on morbidity and mortality in Africa.[3] A major complication of DM is cardiovascular diseases (CVD) which accounts for 22.6% of all deaths.[1] Patients with type 2 diabetes have increased risk of cardiovascular disease due to associated presence of dyslipidaemia.[4] The prevalence of dyslipidaemia in type 2 DM in Nigeria is known to be 89% [5, 6] while in India it is was reported to be 95%.[7] The devastating complication of the lipid-related disease, atherosclerosis, is fast becoming as dreadful as the glucose-centric small vessel disease. Whereas, small vessel disease is very much related to hyperglycaemia, large vessel disease has been difficult to attribute to dysglycaemia.[8,9]

Insulin deficiency has been shown to be associated not only with high serum glucose but also with high serum triglyceride (TG) levels. The degree of dyslipidemia in type 2 DM, particularly hypertriglyceridemia, is exacerbated by poor glycaemic control. Besides the hyperglycaemia, other factors also contribute to the dyslipidaemia seen in DM.[4]

Among these factors is Lipoprotein lipase (LPL) which plays a crucial role in the regulation of lipoprotein metabolism by the hydrolysis of TG-rich particles in muscle, adipose tissue and macrophages thereby generating free fatty acids and glycerol for energy utilisation and storage.[10,11] In 1960, LPL deficiency was discovered by Havel and Gordon,[12] and several mutations were identified upon cloning the gene in 1991 by Henderson *et al*.[13] Subsequently, more subtle mutations were detected in the LPL gene, and some mutants were reputed to influence LPL

activity which has a role in the disease's aetiology.[1,14] Triglycerides and monoglycerides are preferred substrates for LPL, which preferentially hydrolyses 1- and 3-ester bonds in TG, generating 2-monoglycerides, which are converted to 1-monoglyceride by isomerization for further hydrolysis.[15] A small portion of the core TG from chylomicrons and very-low-density lipoprotein (VLDL) can be transferred to high density lipoprotein cholesterol (HDL-C). LPL enzyme activity is insulin-dependent, therefore its activity varies in diabetes according to ambient insulin level. In untreated Type 2 diabetic patients, subnormal LPL activity contributes to the elevation of serum triglycerides and LDL-C as well as reduction of HDL-C level.[16,17]

Elevated cholesterol levels is known to play a key role in both the initiation and progression of atherosclerosis, as well as in the clinical consequences such as myocardial infarction, stroke, peripheral vascular disease, and heart failure.[18]

There is controversy concerning the effect of glycaemic control on the prevalence and pattern of dyslipidaemia in Nigerians with type 2 DM. Agboola-Abu *et al*.[19] reported that improved glycaemic control ameliorated dyslipidaemia in some Nigerian patients with non-insulin dependent diabetes mellitus. However, Akanji *et al*.[20] reported that the higher levels of triglycerides in persons with DM compared with those persons without DM was not influenced by the degree of glycaemic control. Most studies have been carried out in Caucasians and Hispanics. However, few studies done in African-Americans have shown reduced triglyceride level.[21]

To this end, our study aimed to show the relationship between plasma LPL activity and dyslipidaemia in type 2 DM in our local population.

MATERIALS AND METHODS

This was a descriptive cross-sectional study of consenting adult subjects with type 2 diabetes mellitus seen at the Lagos State University Teaching Hospital, Ikeja, located in an urban city in Nigeria, over a three-month duration from January to March 2017.

The study area was the Diabetes Clinic. This clinic attends to approximately 100 patients per Clinic day, average of 15 new patients are seen per day with 2 Clinic days per week. Approval for the study protocol was obtained from the Ethics and Research Committee of the Lagos State University Teaching Hospital. A written informed consent was also obtained from the study participants after adequate explanation of the study. All information obtained during this study was treated as confidential.

Patients who had been diagnosed with type 2 DM according to America Diabetic Association (ADA) [22] and non-diabetic control group were recruited by random sampling. The sampling frame was drawn up by assigning numbers to the patients using patients file record numbers following the order in which they were registered by the Medical Record officers. A table of random numbers was used to select the patients for the study from the file record numbers. A total number of 332 participants were recruited for the study. Patients who had been diagnosed to have type 2 DM according to American Diabetic Association (ADA) [22] or who were on treatment for glycaemic control were included in the study. Patients with hemoglobinopathy, untreated hypothyroidism, Type 1 DM patients on insulin treatment, patients who were receiving any medication known to influence lipid metabolism such as thiazide, beta-blocker, glucocorticoids, oestrogen, HAART, patients with nephrotic syndrome, renal failure, liver disease, alcoholics, cigarette smokers and the obese were excluded from the study. The participants were made to complete a self-administered questionnaire before sample collection.

Participants were made to seat in a comfortable chair for about 10minutes after an overnight fast of about 10-12 hours and venous blood was collected from a peripheral vein through an aseptic procedure. The samples were centrifuged and separated by decanting the supernatant (plasma). The plasma was stored in cryotubes at -80^{o}C in batches for a maximum period of two months before laboratory analysis of LPL activity and lipid profile. The samples collected in EDTA sample bottle was stored as whole blood at 2-8^{o}C for HbA1c analysis within a maximum period of 7 days. Flourimetry principle was used for analysis of LPL activity using Cell Biolabs reagent kit (Avantar, USA); while lipid analysis was done using quantitative-enzymatic reagents (Biolabo SA, Maizy, France) and read by spectrophotometric method. The HbA1c was assayed using ion-exchange chromatographic method with reagents from Fortress Diagnostic, UK, and read spectrophotometrically.

Data Analysis

Data from completed questionnaires and results of LPL activity, Lipid profile and HbA1c were analysed using IBM Statistical Package for Social Sciences version 20.0 (SPSS Inc; Chicago, IL, USA). Kolmogrov-Smirnov test of normality was used to test distribution of data obtained. Distribution of variables was non-Gaussian hence results are expressed as medians (Interquartile range). Comparisons between median values of variables were performed using Mann Whitney U test for unpaired data. Spearman's correlation coefficient was used to determine the association between LPL activity and Total Cholesterol, HDL-C, TG and LDL-C. A p-value of less than 0.05 was considered statistically significant.

RESULTS

A total of three hundred and thirty-two (332) participants were recruited for the study. This comprised of 166 (50%) T2DM patients also known as the test group and 166 (50%) apparently healthy age- and gender-matched controls. The mean age of the test group was 55.6±12.3 years, while the mean age of controls was 53.3±11.5 years ($p = 0.75$).

The male:female (M:F) ratio for the participants was 1:2, while for the control group, was 1:1. There were no statistically significant differences between the participants and controls in the age-group distribution as shown in Table 1.

The test group had a statistically significant higher TC ($p \leq 0.01$) and LDL-C ($p \leq 0.01$) than the controls as indicated in the Table 2. The glycated haemoglobin (HbA1c) level was higher ($p \leq 0.01$) among the T2DM participants than the controls. There was also a statistically significant difference ($p \leq 0.01$) between the lipoprotein lipase activities of the test group when compared to the controls.

We did not find any difference in the triglyceride value

between the participants and the controls. There was no statistically significant difference between the HDL level in test group and the controls (p = 0.45).

Among the test group, there was a weak positive correlation but no statistical significant difference between lipoprotein lipase activity and total cholesterol (r = 0.13, p = 0.10), low density lipoprotein cholesterol (r = 0.12, p = 0.12) and high density lipoprotein cholesterol (r = 0.11, p = 0.18) respectively (Table 3). On the other hand, there was no correlation and no statistically significant difference between LPL activity and triglyceride (r = 0.00, p = 1.00) as seen in Table 3.

In contrast, among the controls, there was a weak negative correlation between LPL and TC (r = -0.14; p = 0.08), as well as between LPL and LDL-C (r = -0.11; p = 0.16). A statistical significant negative correlation exists between LPL and HDL-C (r = -0.34; p ≤ 0.01). We also found a strong positive correlation between LPL activity and triglyceride (r = 0.17; p ≤ 0.03).

Table 1: Age distribution among the test group and controls

Age group	Participants n (%)	Controls n (%)	p-value (≤0.05)
≤39years	24(14.5)	33(19.9)	0.23
40-49years	28(16.9)	30(18.1)	0.79
50-59years	44(26.5)	44(26.5)	1.00
60-69years	53(31.9)	46(27.7)	0.48
70-79years	15(9.0)	12(7.2)	0.56
>80years	2(1.2)	1(0.6)	0.56
Total	166(100%)	166(100%)	0.09
Gender ratio M:F	**1:2**	**1:1**	

Table 2: Biochemical parameters among the test group and controls

Variables	Participants (n=166)	Control (n=166)	p-value (≤0.05)
TC (mg/dl)	185.7±45.1	161.9±44.7	≤0.01
TG (mg/dl)	102.2±74.2	89.6±49.0	0.07
HDL-C (mg/dl)	38.0±11.4	38.9±11.0	0.45
LDL-C (mg/dl)	142.0±43.5	120.5±44.3	≤0.01
HbA1c (%)	8.30±2.4	5.65±0.7	≤0.01
LPL activity (mU/ml)	57.3±3.7	116.9±3.2	≤0.01

Table 3: Association between plasma lipoprotein lipase (LPL) activity and lipid profile in the test group and controls

Variable	Participants (n=166)		Control (n=166)	
	r	p-value	r	p-value
TC (mg/dl)	0.13	0.10	-0.14	0.08
HDL (mg/dl)	0.11	0.18	-0.34	≤0.01
LDL-c (mg/dl)	0.12	0.12	-0.11	0.16
TG (mg/dl)	0.00	1.00	0.17	≤0.03

DISCUSSION

The mean age of the diabetics in our study was slightly above the middle age giving it a similarity to a study of prevalence of DM in a South-western Nigeria town which reported age range value like our study.[23] Also, in a South-south Nigerian study, the mean age was reported to also be slightly above middle age [20] and in a northern Nigerian study, the mean age was similar to our study.[24] The reasons for these similarities could be explained by the diet which are predominantly carbohydrate on a background of a suggested genetic predisposition to DM.[23] Other possible contributory factors include low socio-economic status, poverty, ignorance of the disease, poor state of healthcare system in Nigeria as well as under diagnosis of the disease condition.[20,23] In Nigeria, the risk of developing diabetes mellitus has been reported to increase by 3-4 folds after the age of 44 years.[20]

We found a female preponderance in the mean age group which is similar to the findings in two other studies carried out in South west Nigeria. [23, 25] and another study done in Turkey.[26]

In the female gender, oestrogen has been noted to promote insulin sensitivity, whereas progesterone promotes insulin resistance. Elderly menopausal females therefore have an increased risk of developing diabetes mellitus than men of the same age group.[23, 27] These elderly menopausal women are mostly housewives and pensioners, who visit the hospital more than their male counterparts, [26] and are also more conscious of their health status which may also contribute to this disparity.[25] Studies done in Eastern Nigeria and Ghana also reported a male preponderance of DM [28] attributing it to a poor health-seeking behaviour among the male population as men will only present to the hospital when complications arise.[29] Gender-associated adiposity has also been linked with increased insulin resistance in females. This is different from the central obesity which is commoner in men and which is more predictive of insulin resistance than peripheral obesity.

Many studies have clearly established that complications of diabetes mellitus are mainly due to chronic hyperglycaemia which exerts its injurious effects through several mechanisms including dyslipidaemia, platelet activation and altered endothelial metabolism.[17,26,30] The effect of insulin resistance on adipocytes causes excess lipolysis which is stimulated by hormone-sensitive lipase which eventually causes release of excess free fatty acid (FFA) into the blood and eventually these get to the liver.[31,32] In the liver, the excess delivery of FFA prevents degradation of apolipoprotein B (apo B) thereby up-regulating its concentration. The liver eventually increases production of triglyceride and apo-B rich VLDL.[33] Very low density lipoprotein interacts with LPL in the vessel wall of adipocytes and muscle cells to clear triglycerides for storage in adipocytes and conversion of VLDL to LDL.[34,35] The hypertriglyceridemia may also be initiated by a blunted LPL activity which supports increased hepatic secretion of very low density lipoprotein (VLDL) eventual triglyceride elevation.[33-35] Thirdly, hypertriglyceridemia can result from reduction in LPL activity as a result of poor glycaemic control which combines with increased substrate availability for TG production and subsequently a delayed clearance of triglyceride-rich lipoproteins. [26,36]

Hypertriglyceridemia and Cholesterol Ester Transfer Protein (CETP) cause triglyceride to move to High Density Lipoprotein (HDL) and Low Density Lipoprotein (LDL); and on the other hand cause cholesterol ester to move from HDL and LDL to VLDL. This leads to hypoalphalipoproteinemia and diminution in the size of LDL particle.

The pattern of dyslipidaemia found in this study was

hyperbetalipoproteinaemia and hypercholesterolemia which are both independent risk factors for CVD. Only the hyperbetalipoproteinaemia reported is similar to the findings of a research done in South west Nigeria, same geo-political zone with this index study. [25] They however reported hypoalphalipoproteinemia which is also an independent risk factor for coronary artery disease. Another study found hypertriglyceridemia and hypoalphalipoproteinemia as the most predominant lipid disorders among diabetic patients, attributing their findings to excessive smoking, ingestion of alcoholic beverages and elevated body mass index (BMI).[1]

The non-enzymatic glycosylation of apo B, a process occurring in diabetics because of hyperglycaemia could result in altered LDL metabolism by completely blocking the LDL receptor-mediated LDL catabolism leading to hypercholesterolemia which increases the risk for a coronary artery disease. The beta-lipoproteinemia which represent a high fraction of the total cholesterol will be responsible ultimately for the CVD found in diabetics.[37] Lipoprotein lipase activity has been reported to have pivotal role in the pattern of dyslipidaemia in diabetes mellitus; many researchers have measured lipoprotein lipase activity in diabetes and found that its activity was lower than that of the apparently healthy individuals.[9,15,17] These studies support the finding in this present study, which also reported a low mean LPL activity.

Testosterone, oestrogen and growth hormone have been noted to inhibit adipose tissue LPL activity and promote lipid mobilization. Another factor known to reduce LPL activity include physical inactivity,[38] while LPL activity has been reported to be increased proportionately with fat cell size in the thigh and gluteal region relative to the abdomen giving females a higher LPL activity than the males.[39,40] LPL is a hormone-sensitive enzyme serine hydrolase and a member of the lipase gene family which is responsible for catalysing the ester hydrolysis of triglycerides into free fatty acids. Furthermore, genetic variants such as the Gly188GLU substitution has been noted to have a relatively large effect on decreasing lipoprotein lipase enzyme activity while the more common Asp9Asn and Asn291Ser substitution have a moderate effect in decreasing lipoprotein lipase enzyme activity, leading to hypertriglyceridemia.[41]

A missense mutation *Gly188GLU* within exon 5 has also been noted by some other researchers to be responsible for lipoprotein lipase deficiency.[42] In adipose tissue, one of the main factors regulating LPL activity is the nutrition status of the patient such that in the presence of food, the activity of LPL increases to promote storage of lipids whereas during fasting, the activity of LPL is reduced. Glucose up-regulates the LPL activity of adipose tissues through the glycosylation of LPL which is important for LPL catalytic activity and secretion.[43] LPL activity is insulin-dependent, and therefore varies in diabetes according to ambient insulin level and insulin sensitivity. In diabetic patients with poor glycaemic control, subnormal LPL activity may contribute to dyslipidaemia.[9] This is in keeping with expected findings of low LPL activity in type 2 diabetics as in this study and can eventually predispose to cardiovascular diseases through the dyslipidaemia. Based on the regulatory effects of diet and exercise on LPL activity, the values obtained from this study may have been affected by the regular lifestyle of the patient as well as the management modalities prescribed for each of the patient. It is expected that patients who subject themselves to starvation or starvation diet and are not involved in any form of physical activity may have a reduced LPL activity and vice versa.[38-40]

In this study, the LPL activity increased with hyperlipidaemia with the exception of triglycerides in T2DM participants and this contrasts with the picture in healthy individuals. This could be attributed to the fact that there are other factors like genetic variance of LPL activity contributing to dyslipidaemia in type 2 diabetics.[41,42]

The relationship of LPL activity and dyslipidaemia in type 2 diabetes mellitus has been shown to be indirectly proportional.[7] However, hypercholesterolemia is still a common finding in a good number of diabetic and may be an independent risk factor for cardiovascular diseases.

Insulin deficiency decreases the liver apolipoprotein B production which in-turn regulates the activity of LPL and cholesterol ester transport protein.[10] Insulin deficiency also reduces the activity of hepatic lipase and several other metabolic steps in the production of biologically active lipoprotein lipase which is altered in DM.

The overall effect of insulin deficiency affects lipid and apo-protein metabolism, LPL activity as well as tissue-specific substrate delivery and utilization, with a resultant affectation of energy balance, dyslipidaemia and antecedent risk of cardiovascular disease.

Insulin deficiency and/or resistance is associated with decreased LPL activity which is known to influence the transport and metabolism of lipid with resultant various dyslipidaemia pattern which may as independent or combined risk factors lead to cardiovascular disease.

Reduced activity of LPL would therefore be a reason for lipoprotein size and sub-classes examination in view of the no significant increase in the serum HDL-C level of diabetics.

This information will guide physicians in the follow up management as well as prevention of cardiovascular and atherosclerotic diseases.

Limitations of this Study

The limitations of this study included the short half-life of reagents in-relation to the recruitment duration and the inability to study the genetic variants of LPL in diabetics which would have answered more questions and probably break new grounds as to the exact relationship between the LPL enzyme and dyslipidaemia .

Recommendations

We recommend that there is a need for all diabetes mellitus patients to be assessed or screened at least annually for their pattern of dyslipidaemia in addition to the routine monitoring of their glycaemic control. However, further studies should be carried out to determine the genetic variance of LPL activity in our locality. These are all in the overall interest of reducing the morbidity and mortality of the CVD associated complications in diabetes mellitus

Conflict of Interest

The authors declare no competing interests.

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