DYSLIPIDEMIA PROFILE OF TYPE 2 DIABETIC PATIENTS ATTENDING STATE HOSPITAL IN ILARO, NIGERIA

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Abstract
Dyslipidemia is a common feature of diabetic patients, and this condition is a risk factor for the development of cardiovascular diseases. The dyslipidemia patterns were investigated in diabetic patients undergoing medical and dietary treatment. Diabetic patients attending the Diabetes Clinic in State Hospital, Ilaro, Nigeria were recruited into the study after their informed consent. Both anthropometric and biochemical analysis was conducted. Both diabetic normotensive (DBN) and diabetic hypertensive (DBH) subjects had significantly reduced ($p < 0.05$) plasma phospholipids and high density lipoprotein cholesterol (HDL-C), as well as significantly increased ($p < 0.05$) concentration of plasma glucose and low density lipoprotein cholesterol (LDL-C) compared to the non-diabetic subjects. Atherogenic indices (LDL-C/HDL-C and TG/HDL-C) were also significantly elevated ($p < 0.05$) in the diabetic subjects compared to the other groups. This study suggests that dyslipidemia occurred in these diabetic patients due to complications from diabetes mellitus, and this may predispose them to cardivascular diseases like atherosclerosis.

Keywords: Dyslipidaemia, HDL-cholesterol, phospholipids, hypercholesterolemia, diabetes, LDL-cholesterol.

INTRODUCTION
Dyslipidemia refers to the derangement of one or more of the blood lipoproteins leading to the disequilibrum of lipids concentration within the blood (Misra and Vikram, 2004). Lipids are essential to life, but an excess of certain lipids can increase the risk of cardiovascular disease (Poirier *et al*., 2006). In dyslipidemia, the level of one or more of these lipids is abnormal (Poirier *et al*., 2006). The lipids that are normally measured within the blood include various forms of cholesterol, as well as triacylglycerol. It may manifest as one or more of the following: elevated total cholesterol, low-density lipoprotein cholesterol (LDL-C), and triacylglycerol levels or as decreased high density lipoprotein cholesterol (HDL-C) level with promotion of insulin resistance (Misra *et al*., 2005).

Dyslipidemia may be as a result of single or multiple genetic mutation that ends up in either overproduction or defective clearance of triglycerides and LDL-C or underproduction or excessive clearance of HDL-C (Rader and Hobbs, 2007). The

foremost vital secondary reason behind dyslipidemia is inactive life style with excessive dietary intake of saturated fat and cholesterol (Mahley *et al*., 2008). Other secondary causes include diabetes mellitus, alcohol intake, chronic kidney disease, hypothyroidism, primary biliary cirrhosis and other cholestatic liver diseases as well as drugs such as thiazides, β-blockers, retinoids, highly active antiretroviral agents, estrogen and glucocorticoids (Mahley *et al*., 2008). Diabetes induced dyslipidemia is not as a result of hyperglycemia intrinsically but primarily as a consequential effect of the defect in lipid metabolism due to insulin resistance. This is so because dyslipidemia is often found in prediabetics and in patients with insulin resistance (e.g., obese patients) but with regular concentration of plasma glucose (Haffner *et al*., 2000).

Though several studies have been conducted on diabetic subjects, there is a dearth of information on the dyslipidemia pattern of diabetic patients. Therefore, this study was aimed at finding the dyslipidemia pattern of diabetic patients receiving both medical and dietary treatment in Ogun State, Nigeria.

MATERIALS AND METHOD

Chemicals and reagents

The assay kits for the determination of glucose, total cholesterol (TC), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C) and triglycerides (TG) were obtained from Randox Laboratories, Antrim BT41, United Kingdom. All other chemicals were of analytical grade and water was glass distilled.

Experimental design

Diabetic patients attending the Diabetes Clinic in State Hospital, Ilaro (Ogun State, Nigeria.) were recruited into the study after their informed consent. A close-ended questionnaire was administered to each patient detailing their lifestyle, eating and drinking pattern as well as family history. Exclusion factors were known patients with any form of diabetic complications and smokers, and patients with family history of hyperlipidemia. Patients who were severely obese or had thyroid, kidney or liver disease and those taking steroids, β -blockers, diuretics, or hypolipidemic drugs were also excluded.

The age range of the subjects was between 20 - 70 years and body mass index (BMI) of the patients were considered. This study was conducted on 111 diabetic patients and 33 non-diabetic controls. The diabetics were stratified into diabetic normotensive (n = 16; 8 males and 8 females) and diabetic hypertensive (n = 95; 32 males and 63 females) and the controls into non diabetic normotensive (n = 19; 10 males and 9 females) and non diabetic hypertensive (n = 14; 8 males and 6 females). Anthropometric parameters like weight, height, body mass index (BMI) and waist circumference were determined. Systolic and diastolic blood pressures were also taken. About 2% of the diabetics were

recently diagnosed and were not on any drug while the remaining 95% were on antidiabetic drugs like metformin, glibenclamides and antihypertensive like vasoprin, simvastatin and nifedipine.

Determination of biochemical parameters

Lipids and lipoproteins concentration were determined in plasma samples obtained from blood drawn after 12 h overnight fast. Plasma total cholesterol (TC), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C) and triglycerides (TG) were measured by enzymatic methods using commercially available assay kits from Randox Laboratories, UK (Hu *et al*., 2008). Plasma phospholipid was analysed colorimetrically (Kim *et al*., 2013) while plasma fasting glucose was assayed using enzymatic glucose oxidase method of Klonoff (2005). Glucose oxidase catalysed the oxidation of glucose to form gluconic acid and hydrogen peroxide. The LDL-C/HDL-C and TG/HDL-C ratios were simply calculated from the respective values of LDL-C, HDL-C and TG.

Statistical analysis

Statistical analysis was performed using GraphPad Prism 5 statistical package (GraphPad Software, San Diego MA, USA). The data were analysed by one way analysis of variance (ANOVA) followed by Tukey test. All the results were expressed as mean ± SEM and were considered statistically significant when $p < 0.05$.

RESULTS

Table 1 shows the anthropometric parameters of the subjects recruited for this study. The ages, weights and BMI of the female non-diabetic normotenisve subjects were significantly reduced ($p < 0.05$) compared to females of other groups. The male diabetic normotensive subjects also differ significantly ($p < 0.05$) in its weight, height and BMI in comparison to other groups. The height of the female diabetic hypertensive patients was significantly reduced ($p < 0.05$) compared to other subjects while the ages of male non-diabetic patients (NDN and NDH) were different from the male diabetic patients (DBN and DBH).

Table 1: Anthropometric parameters of non-diabetic and diabetic subjects used in this study

Group	Age		Weight		Height		BMI	
	Male	Female	Male	Female	Male	Female	Male	Female
NDN	41.10 ± 8.90[a]	36.00 ± 7.50[a]	62.70 ± 5.10[a]	56.20 ± 8.60[a]	1.62 ± 0.10[a]	1.51 ± 0.10[a]	23.90 ± 3.78[a]	24.54 ± 3.21[a]
NDH	46.00 ± 9.44[a]	49.67 ± 9.30[b]	67.80 ± 7.40[a]	72.70 ± 9.90[b]	1.66 ± 0.10[a]	1.59 ± 0.10[a]	24.82 ± 6.42[a]	28.92 ± 5.89[b]
DBN	27.00 ± 7.10[b]	51.83 ± 8.30[b]	57.00 ± 5.00[b]	66.33 ± 4.70[b]	1.75 ± 0.00[b]	1.55 ± 0.03[a]	18.60 ± 0.00[b]	27.65 ± 1.74[b]
DBH	58.90 ± 7.50[c]	54.87 ± 6.60[b]	71.10 ± 9.00[a]	73.52 ± 8.60[b]	1.66 ± 0.10[a]	1.66 ± 0.08[b]	25.93 ± 3.65[a]	29.50 ± 5.63[b]

Values are mean ± SEM. Test values down vertical columns carrying different superscript are significantly different ($p < 0.05$).

NDN: Non-diabetic normotensive, NDH: Non-diabetic hypertensive, DBN: Diabetic normotensive, DBH: Diabetic hypertensive, BMI: Body mass index

The systolic and diastolic blood pressures of the subjects is shown in Table 2. Systolic and diastolic blood pressures of all non-diabetic hypertensive and diabetic hypertensive subjects were significantly higher ($p < 0.05$) than that of both non-diabetic normotenisve and diabetic normotensive subjects. This trend cut across both the male and female groups.

Table 2: Systolic and diastolic blood pressures of both non-diabetic and diabetic subjects used in this study

Group	Systolic		Diastolic	
	Male	Female	Male	Female
Non-diabetic normotensive	109.30 ± 15.79[a]	102.00 ± 4.47[a]	71.30 ± 7.38[a]	66.70 ± 5.48[a]
Non-diabetic hypertensive	130.25 ± 13.48[b]	125.83 ± 9.17[b]	80.88 ± 6.58[b]	83.35 ± 1.65[b]
Diabetic normotensive	99.40 ± 5.10[a]	105.67 ± 7.83[a]	77.00 ± 4.20[a]	67.57 ± 4.08[a]
Diabetic hypertensive	137.91 ± 20.14[b]	135.48 ± 17.02[b]	83.34 ± 10.27[b]	82.83 ± 9.95[b]

Values are mean ± SEM. Test values down vertical columns carrying different superscript are significantly different ($p < 0.05$).

Figure 1 shows the fasting plasma glucose, total cholesterol, triglyceride and phosphoglyceride concnetration of diabetic and non-diabetic subjects. There was no significant difference in the glucose concentration of the non-diabetic normotensive and non-diabetic hypertensive groups, but diabetic normotensive and diabetic hypertensive groups witnessed significant increase ($p < 0.05$) compared to the non-diabetic groups (Figure 1a). The total cholesterol concentration of diabetic hypertensve subjects was significantly higher ($p < 0.05$) than other groups, while the results of other groups were

similar to one another (Figure 1b). The diabetic normotensive and diabetic hypertensive subjects respectively exhibited significantly lower and higher triacylglycerol concentration compared to non-diabetic groups (Figure 1c). The phospholipid concentration was similar in both non-diabetic normotensive and non-diabetic hypertensive groups, just as in comparing diabetic normotensive and diabetic hypertensive group to each other (Figure 1d). However, phospholipid concentration was significantly decreased ($p < 0.05$) in the diabetic groups compared to the non-diabetic ones.

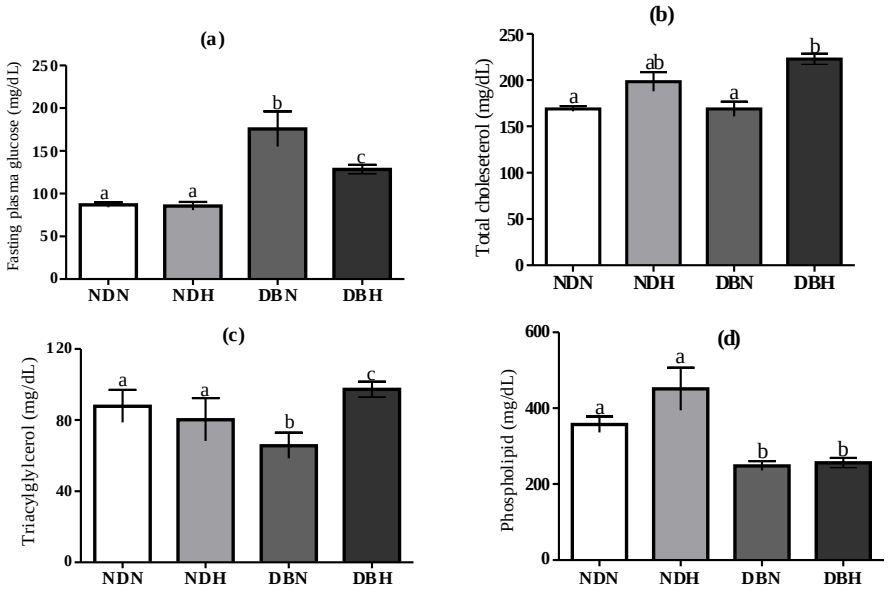

Figure 1: (a) Fasting blood glucose, (b) total cholesterol, (c) triglyceride and (d) phosphoglyceride concentration of non-diabetic and diabetic subjects. Bars with different letters are significantly different ($p < 0.05$).

NDN: Non-diabetic normotensive, NDH: Non-diabetic hypertensive, DBN: Diabetic normotensive, DBH: Diabetic hypertensive

Figure 2 shows the LDL-cholesterol concentration, HDL-cholesterol concentration, as well as LDL-C/HDL-C and TG/HDL-C ratios. The diabetic hypertensive subjects possesed significantly higher ($p < 0.05$) LDL-cholesterol concentration compared to the non-diabetic groups. However, diabetic normotensive subjects were similar to values obtained for other groups (Figure 2a).

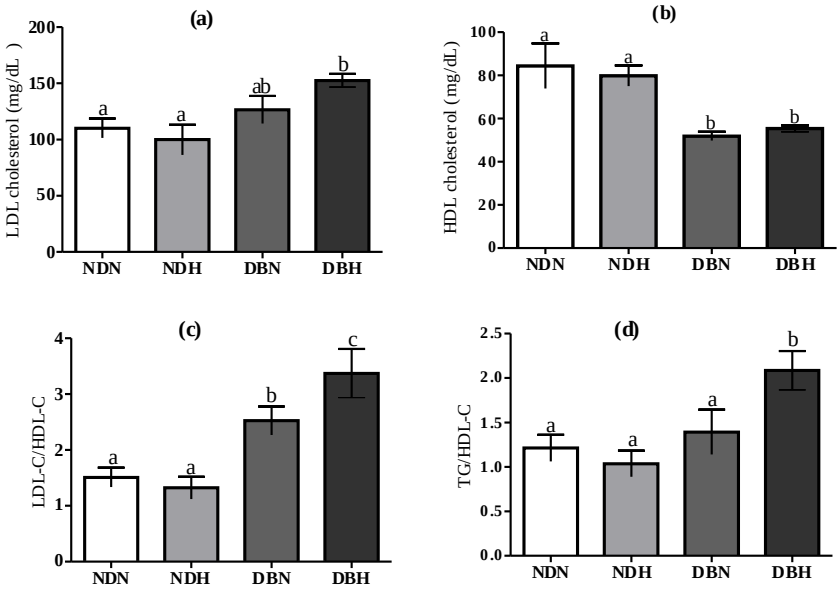

Figure 2: (a) LDL cholesterol concentration, (b) HDL cholesterol concentration, (c) LDL-C/HDL-C ratio and (d) TG/HDL-C ratio of non-diabetic and diabetic subjects. Bars with different letters are significantly different ($p < 0.05$).

NDN: Non-diabetic normotensive, NDH: Non-diabetic hypertensive, DBN: Diabetic normotensive, DBH: Diabetic hypertensive, LDL-C: Low density lipoprotein cholesterol, HDL-C: High density lipoprotein cholesterol, TG: Triglyceride

The HDL-cholesterol concentration was significantly elevated ($p < 0.05$) in both groups of non-diabetic subjects compared to their diabetic counterparts, but there was no difference between the non-diabetic normotensive and non-diabetic hypertensive subjects as well as between the diabetic normotensive and diabetic hypertensive groups (Figure 2b). Diabetic hypertensive subjects displayed significantly higher ($p < 0.05$) LDL-C/HDL-C ratio, followed by the diabetic normotensive subjects compared to other groups. Both non-diabetic normotensive and non-diabetic diabetic hypertensive group were similar to each other. (Figure 2c). Diabetic hypertensive subjects also possessed significant elevation in TG/HDL-C ratio compared to all other groups, while other groups were similar to one another (Figure 2d).

DISCUSSION

Diabetes mellitus is characterized by derangement in carbohydrate, protein and lipid metabolism which is diagnosed majorly by increase in blood glucose concentration (hyperglycemia) (Kazeem *et al*., 2015). The observed elevation in the plasma glucose concentration of the diabetic groups, may be due to insulin resistance or insensitivity by the cell membrane receptors in the diabetics compared to the non-diabetic group that has

normal insulin sensitivity. Glucose is not well metabolized by the cells of the diabetics since it cannot be driven into the cells as result of insulin resistance or insensitivity to glucose by cell membrane receptors (Unger and Orci, 2010).

Previous studies have shown that diabetes is associated with alterations in the plasma lipid and lipoprotein profile, due to hyperglycemia (Maghrani et al., 2004; Krauss, 2004). The difference in total cholesterol concentration between the diabetic hypertensive and other groups may be attributed to the combined effects of diabetes and hypertension. This may be connected to defective lipid metabolism as they cannot properly regulate cholesterol synthesis intracellularly via sterol regulatory element binding protein 2 (SREBP-2) (Pihlajamäki *et al*., 2004). Therefore in insulin-resistant states such as obesity, metabolic syndrome and type 2 diabetes, cholesterol synthesis is upregulated, and cholesterol absorption efficiency is low.

Triacylglycerol functions as one of the energy reservoirs in man (Voet *et al*., 2016). The observed increase in the triacylglycerol concentration of diabetic hypertensive subjects compared to other groups is a common feature of type 2 diabetes mellitus. This corroborates the findings of Khan *et al*. (2008). Insulin modulates triglyceride levels, partly by inducing lipoprotein lipase, which contributes to the clearance of chylomicron-triacylglycerol (Kazeem *et al*., 2015). The rate of chylomicron clearance mostly determines fasting and postprandial triacylglycerol levels in patients with diabetes. However, many different metabolic abnormalities seem to contribute to diabetic hypertriglyceridaemia, together with increased plasma VLDL concentrations (with or without chylomicronaemia), increased cholesteryl ester transfer protein activity and increased hepatic flux of free fatty acids (Krauss, 2004).

Phospholipid is a class of lipids which are major components of cell membrane and maintain cholesterol homeostasis as well as triacylglycerol secretion and storage (Lagace and Ridgway, 2013). The reduced concentration of total plasma phospholipids observed in the diabetics compared to the non-diabetic subjects may be due to low levels of dihomo-γ-linolenic acid, arachidonic acid, α-linolenic acid and docosahexaenoic acid, experienced in diabetic patients (Hodge *et al*., 2007). This is because dihomo-γ-linolenic acid and arachidonic acid are precursors of prostaglandin E1 (PGE1) and prostacyclin (PGI2), which are potent platelet anti-aggregators and vasodilators and can prevent thrombosis and atherosclerosis that will lead to hypertension (Das, 2008).

The higher concentration of LDL-cholesterol in the diabetic hypertensive subjects is expected because this group have more oxidized low density lipoprotein that forms foam cells and subsequently, plaque that leads to diabetes-induced hypertension (Nakhjavani *et al*., 2010). Insulin deficiency or insulin resistance may also be responsible for this because insulin has an inhibitory action on β-hydroxyl-β-methyl glutaryl CoA reductase (HMG-CoA reductase), a key rate-limiting enzyme responsible for the metabolism of

cholesterol-rich LDL particles (Kumar *et al*., 2005). This causes increase in fatty acid mobilization from adipose tissues and results in increased production of cholesterol-rich LDL particles. The similarity between the LDL-cholesterol of non-diabetic groups and diabetic normotenisve group may be attributed to strict compliance with of the subjects to hypoglycemic control (Murali *et al*., 2002). This is because oral hypoglycemic agents (e.g metformin) has been shown to have ability to reduce LDL-cholesterol and triacylglycerol concentration (Bolen *et al*., 2007; Maharani, 2009; Wolffenbuttel *et al*., 2005).

HDL-C is an anti-atherogenic lipoprotein which transports cholesterol from peripheral tissues into the liver. The HDL-cholesterol concentration of the non-diabetic groups was higher than the diabetic groups, which is in consonance with the findings of Lorenzo *et al*. (2010). This study indicated positive significant association between elevated blood glucose concentrations and low concentrations of HDL-C. Hyperglycemia progressively increases the transfer of cholesterol esters from HDL-C to LDL-C particles (Parikh *et al*., 2010). In addition, HDL-C is a ready substrate for hepatic lipase that converts it into smaller particles that are readily cleared from the plasma. The relative insulin deficiency that occurs in type 2 diabetes impairs the action of lipoprotein lipase and results in lower HDL-C levels and higher TG levels, which may improve with improved glycemic control (Wang and Peng, 2011). Thus, HDL hypocholesterolemia in type 2 diabetic patients is mainly due to insulin resistance-linked lipoprotein lipase deficiency (Rader and Tall, 2012).

In individuals with diabetes, cardiovascular risk is increased by a cluster of factors such as abdominal obesity, impaired fasting glucose, increased blood pressure, low HDL-C, increase in both TGs and LDL-C particles (International Diabetes Federation, 2009). Although, insulin resistance is crucial to the pathogenesis of this disease, the associated atherogenic lipoprotein phenotype considerably enhances the risk (da Luz *et al*., 2008). Thus there was the necessity to gauge atherogenic indices from the lipid profile obtained during this study. Many lipoprotein-related indices are postulated to evaluate the chance of cardiovascular diseases in diabetes, which include LDL-C/HDL-C and TG/HDL-C ratios, and are adjudged to be good predictive value for future cardiovascular events (Fisher *et al*., 2012). The higher values of atherogenic indices (LDL-C/HDL-C and TG/HDL-C) experienced diabetic groups may be due decreased HDL-C and increased LDL-C concentration, which are all connected to derangements in lipid metabolism.

CONCLUSION

The major dyslipidemia observed in diabetic subjects was in reduced phospholipid and HDL-cholesterol, as well as increased LDL-cholesterol concentration. This pattern is a reflection of continuous diabetic control through the administration of antidiabetic drugs. It is therefore recommended that diabetics have their lipid profile checked in addition to glucose level, in order to monitor possible complications that may arise due to dyslipidemia. The non-diabetic hypertensive group also exhibited hypercholesterolemia

which is undesirable. Non-diabetic individuals should always undergo medical checkup in order to monitor their lipid profile and by extension.

CONFLICT OF INTEREST

The authors declare there is no conflict of interest regarding this study.

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