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Effect of Treatment Duration of Type 2 Diabetes Mellitus on Lipid Profile in Hausa/Fulani

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Abstract **Original Research Article**

Dyslipidaemia is a common feature of type 2 diabetes mellitus. Classical findings are increased in level of total cholesterol, triglyceride and low-density lipoprotein with associated decreased in high density lipoprotein, insulin resistance plays major in this process. Dyslipidemia is a metabolic abnormality mostly associated with diabetes mellitus. Derangement in lipid metabolism have been reported in patients with diabetes mellitus accompanied by the risk of cardiovascular arteriosclerosis. In diabetes a lot of factors could affect serum lipid level, due to interrelationship between carbohydrates and lipid metabolism. This study was carried out to know the effect of duration treatment of type 2 diabetes mellitus on lipid profile in Hausa/Fulani. The study was a cross sectional one carried out at Specialist Hospital, Sokoto from June to December 2018. The patients were assessed, the assessments include history (a questionnaire) and clinical examination. Lipid profile was determined in one hundred (100) diabetic subjects and one hundred (100) non-diabetic subjects using enzymatic colorimetric method. The diabetic patients were grouped into five groups. Group A1. Treatment naïve. Group A2. on treatment for less than a year (<1yr). Group A3. on treatment for one to less than two years (1 - <2yr). Group A4. on treatment for two to less than five years (2 - <5yr). Group A5. On treatment for five years and above (≥ 5yr). The mean concentration of (TG) in group A4 (170.04±22.38mg/dL) and group A5 (193.58±15.83) were significantly higher compared to group A2, A3 and control ($p<0.05$). Also, the concentration of (LDL) in group A5 (113.85±5.48mg/dL) and A4 (104.45±7.75mg/dL) were significantly higher compared to group A3, A2 and control. However, the mean concentration of (HDL) in control group (91.22±2.28mg/dL) were significantly higher compared to all the diabetic subjects. As the duration of treatment of diabetes mellitus increases, abnormal lipid metabolism also increases.

Keywords: Type 2 diabetes mellitus, lipid profile, Dyslipidaemia, Hausa/Fulani.

INTRODUCTION

Type 2 diabetes mellitus (also known as non-insulin -dependent diabetes mellitus (NIDDM) refers to patients with diabetes mellitus characterized by insulin resistance or a state of relative insulin deficiency [1]. Clinical studies will often use diabetes onset after age of 30 years as an operational criterion for type 2 diabetes mellitus [1]. Type 2 diabetes mellitus is insidious and may be present for years before being diagnosed [2]. Approximately, a good percentage of all diagnosed cases of diabetes mellitus is Type 2 and may be as many undiagnosed cases of Type 2 as diagnosed cases [2].

Dyslipidaemia is a common feature of type 2 diabetes mellitus [3]. Classical findings are increased in level of total cholesterol, triglyceride and low-density lipoprotein with associated decreased in high density lipoprotein, insulin resistance plays major in this process [4]. Dyslipidemia is a metabolic abnormality mostly associated with diabetes mellitus [4]. Derangement in lipid metabolism have reported in patients with diabetes mellitus accompanied by the risk of cardiovascular arteriosclerosis [3]. In diabetes a lot of factors could affect serum lipid level, due to interrelationship between carbohydrates and lipid metabolism [5]. Consequently, any disorder in carbohydrate metabolism can result to disorder in lipid metabolism and vice versa [6]. Insulin resistance is a primary defect in the majority of subjects with type 2 diabetes mellitus [7]. Many studies have shown that insulin affects the liver apolipoprotein production and regulates the enzymatic activity of lipoprotein lipase and cholesterol ester transport protein, which causes dyslipidemia in diabetes [8]. However, insulin

deficiency reduces the activity of hepatic lipase and several steps in production of biologically active lipoprotein lipase [9].

TRIGLYCERIDE

A triglyceride (TG) is an ester derived from glycerol and three to four fatty acids (from *tri-* and *glyceride*) [10]. Triglycerides are the main constituents of body fat in humans and other animals, as well as vegetable fat [11]. They are also present in the blood to enable the bi-directional transference of adipose fat and blood glucose from the liver, and are a major component of human skin oils [12].

There are many different types of triglyceride, with the main division between saturated and unsaturated types [13]. Saturated fats are "saturated" with hydrogen, all available places where hydrogen atoms could be bonded to carbon atoms are occupied. These have a higher melting point and are more likely to be solid at room temperature [14]. Unsaturated fats have double bonds between some of the carbon atoms, reducing the number of places where hydrogen atoms can bond to carbon atoms. These have a lower melting point and are more likely to be liquid at room temperature [13].

Chemical Structure

Triglycerides are chemically tri esters of fatty acids and glycerol [15]. Triglycerides are formed by combining glycerol with three fatty acid molecules. Alcohols have a hydroxyl (HO-) group. Organic acids have a carboxyl (-COOH) group. Alcohols and organic acids join to form esters [16]. The glycerol molecule has three hydroxyls (HO-) groups. Each fatty acid has a carboxyl group (-COOH). In triglycerides, the hydroxyl groups of the glycerol join the carboxyl groups of the fatty acid to form ester bonds [16]:

$$HOCH_2CH(OH)CH_2OH + RCO_2H + R'CO_2H + R''CO_2H \rightarrow RCO_2CH_2CH(O_2CR')CH_2CO_2R'' + 3H_2O$$

The three fatty acids (RCO_2H, $R'CO_2H$, $R''CO_2H$ in the above equation) are usually different, but many kinds of triglycerides are known [17]. The chain lengths of the fatty acids in naturally occurring triglycerides vary, but most contain 16, 18, or 20 carbon atoms [18]. Natural fatty acids found in plants and animals are typically composed of only even numbers of carbon atoms, reflecting the pathway for their biosynthesis from the two-carbon building-block acetyl CoA. Bacteria, however, possess the ability to synthesis odd-and branched-chain fatty acids [19]. As a result, ruminant animal fat contains odd-numbered fatty acids, such as 15, due to the action of bacteria in the rumen. Many fatty acids are unsaturated, some are polyunsaturated (e.g., those derived from linoleic acid) [20].

Most natural fats contain a complex mixture of individual triglycerides. Because of this, they melt over a broad range of temperatures. Cocoa butter is unusual in that it is composed of only a few triglycerides, derived from palmitic, oleic, and stearic acids in the 1-, 2-, and 3- positions of glycerol, respectively [21].

Role in Disease

In the human body, high levels of triglycerides in the bloodstream have been linked to atherosclerosis and, by extension, the risk of heart disease and stroke [22]. However, the relative negative impact of raised levels of triglycerides compared to that of LDL:HDL ratios is as yet unknown [23]. The risk can be partly accounted for by a strong inverse relationship between triglyceride level and HDL-cholesterol level [23].

LOW-DENSITY LIPOPROTEIN (LDL)

Low-density lipoprotein (LDL) are one of the five major groups of lipoproteins which transport all fat molecules around the body in the extracellular water [24]. These groups, from least dense, compared to surrounding water, (largest particles) to most dense (smallest particles), are chylomicrons (aka ULDL by the overall density naming convention), very low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), low-density lipoprotein and high-density lipoprotein (HDL) [25]. LDL delivers fat molecules to the cells and can drive the progression of atherosclerosis if they become oxidized within the walls of arteries [26].

LDL particles pose a risk for cardiovascular disease when they invade the endothelium and become oxidized, since the oxidized forms are more easily retained by the proteoglycans. A complex set of biochemical reactions regulates the oxidation of LDL particles, chiefly stimulated by presence of necrotic cell debris and free radicals in the endothelium. Increasing concentrations of LDL particles are strongly associated with the development of atherosclerosis and hence endothelial dysfunction over time [26].

LDL particles are formed as VDL lipoproteins lose triglyceride through the action of lipoprotein lipase (LPL) and they become smaller and denser (i.e. fewer fat molecules with same protein transport shell), containing a higher proportion of cholesterol esters.

When a cell requires additional cholesterol (beyond its current internal HMG CoA production pathway), it synthesizes the necessary LDL receptors as well as PCSK9, a pro-protein convertase that marks the LDL receptor for degradation. LDL receptors are inserted into the plasma membrane and diffuse freely until they associate with clathrin-coated pits. When LDL receptors bind LDL in the bloodstream, the clathrin-coasted pits are endocytosed in the cell [27].

Vesicles containing LDL receptors bound to LDL are delivered to the endosome [28]. In the presence of low pH, such as the found in the endosome, LDL receptors undergo a conformation change, releasing LDL. LDL is then shipped to the lysosome, where cholesterol esters in the LDL are hydrolysed. LDL receptors are typically returned to the plasma membrane, where they repeat this cycle. If LDL receptors bind to PCSK9, however, transport of LDL receptors is redirected to the lysosome, where they are degraded [29].

Role in the Innate Immune System

LDL interfere with the quorum sensing system that upregulate genes required for invasive staphylococcus aureus infection. The mechanism of antagonism entails binding Apolipoprotein B to a *S. aureus* autoinducer pheromone, preventing signaling through its receptor. Mice deficient in apolipoprotein B are more susceptible to invasive bacterial infection.

Hypertriglyceridaemia usually accompanies fall in HDL cholesterol, which is also a significant feature of plasma lipid abnormalities seen in individuals with diabetes [30]. This study was carried out to know the effect of treatment duration of type 2 diabetes mellitus on lipid profile in Hausa/Fulani.

MATERIALS AND METHODS

The research was carried out in the Department of Chemical Pathology and Immunology, College of Health Sciences (CHS) and Department of Medicine Specialist Hospital Sokoto. A total of 200 participants were consecutively selected for the study. Only diabetic and apparently healthy individuals who fulfilled the inclusion criteria and agreed to participate in the study were selected. Diabetic subjects were selected from diabetic clinics in the Department of Medicine Specialist Hospital, Sokoto. Preliminary information such as age, sex, height, weight of the patients, duration of the disease and medications were obtained using a questionnaire. Patients that were only dieting as means of diabetic controls were also noted. The control subjects were 100 apparently healthy individuals, of both genders. Those with history of liver diseases and cigarette smoking were excluded from the study. Type 2 diabetic patients and apparently healthy individuals aged 18 years to 60years were recruited into the study. Type 1 diabetic patient, Hypertensive patient, Diabetic patient with coexisting other endocrine disorders and Diabetic patient that consume alcohol were excluded from the study. Individuals who were non-diabetic and who have never had any family history of diabetes were included in the study as controls. Participants (Diabetics patients and apparently healthy controls) were fully informed, and their consent were obtained before the commencement of the research. Participants were allowed to withdraw from the study at any time and for any reason. Approval was obtained from the Ethics and Research Committee of the Specialist Hospital Sokoto. The study was a descriptive cross-sectional study, which was performed on Diabetic subjects attending Diabetic Clinic at Specialist Hospital Sokoto, for a period of 12 months. The research was carried out on diabetic subjects and apparently healthy individual serve as controls. The diabetic patients were categorized into 2; group A based on duration of treatment and group B, which served as control. Group A was further subclassified into 5.

Group A1. Treatment naïve
Group A2. on treatment for less than a year (<1yr)
Group A3. on treatment for one to less than two years (1 - <2yr)
Group A4. on treatment two to less than five years (2 - <5yr)
Group A5. On treatment for five years and above (≥ 5yr).

Eight milliliter (6ml) of whole blood was collected from each diabetic subjects and controls. Four milliliter (2ml) from this was placed in EDTA bottles for glycated haemoglobin, Two milliliter (2ml) was placed in a fluoride-oxalate container for fasting plasma glucose assay. The remaining Two milliliter (2ml) was placed in plane sample bottles for lipid profile assay. The latter was centrifuged at 4°C and the plasma was collected and preserved for fibronectin assay. The EDTA samples was stored at 2^{o} C and analyzed the following day for glycated haemoglobin while the fluoride-oxalate samples were centrifuged immediately and the samples analyzed for plasma glucose.

STATISTICAL ANALYSIS

The data obtained were analyzed using Microsoft Office Excel 2007 and SPSS software version 20.0 of 2016. The results of plasma fasting glucose and lipid profile obtained from diabetic subjects were compared with the controls using pair two-tailed student's t-test for matched samples, while analysis of variance (ANOVA) was used to for comparisons of three (3) or more mean values of the parameters in the various groups. In each case where there was significant difference, a post-hoc analysis was carried out using Bonferroni multiple comparisons test. A p-value of less than or equal to 0.05 ($P \leq 0.05$) was considered as statistically significant.

RESULTS

A total of two hundred (200) subjects participated in this study. Of this number, 100 were diabetic patients, 45 males (45%) and 55 females (55%) with their age ranged between 20 and 60years and mean age and standard error of mean of (49.53±0.92). The remaining 100 were age and sex matched apparently healthy individual comprised of 48 males (48%) and 52 female (52%) who served as controls.

The anthropometric data of the diabetic subjects were summarized in table 4.2, the age, body

weight, BMI and diastolic blood pressure of the diabetic were found to be similar with the control ($p>0.05$). However, the systolic blood pressure and height of the diabetic subjects was significantly higher than the control ($p<0.05$).

Table-1: Anthropometric Data of the Diabetic Subjects (Mean ± SEM)

Characteristics	Group A Diabetic Patients (n=100)	Group B Controls (n=100)	P value
Male	45	48	
Female	55	52	
Age (Years)	49.53 ± 0.92	45.9 ± 1.48	0.457
Sbp (mmHg)	115.59 ± 0.84^{b}	111.30 ± 1.54^{a}	0.009
Dbp (mmHg)	74.24±0.77	73.24±1.10	0.460
Body Weight (Kg)	68.11±1.70	65.98±2.62	0.485
Height(m)	1.62 ± 0.01^{b}	1.72 ± 0.01^{a}	0.000
BMI(Kgm^{-2})	27.19 ± 0.63	25.14 ± 0.82	0.056

Values are expressed as Mean ± SEM; Values of the group with superscript "a" are statistically significantly ($p<0.05$) and different from group A. Values of the group with superscript "b" are statistically significantly ($p<0.05$) and different from group B.

Table-2 shows the mean concentration of fasting blood glucose (FBG), Total cholesterol (TC), Triglyceride (TG), High Density Lipoprotein (HDL) and Low-Density Lipoprotein (LDL) in diabetic subjects based on treatment duration and controls. The mean concentration of (FBG) in group A5 (10.70±0.65mmol/L), group A4 (11.00±0.92mmol/L), group A3 (11.37±1.25mmol/L) were significantly higher ($p<0.05$) compared to control. The mean concentration of (TG) in group A4 (170.04±22.38mg/dL) and group A5(193.58±15.83) were significantly higher compared to group A2, A3 and control ($p<0.05$). Also, the concentration of (LDL) in group A5 (113.85±5.48mg/dL) and A4 (104.45±7.75mg/dL) were significantly higher compared to group A3, A2 and control. However, the mean concentration of (HDL) in control group (91.22±2.28mg/dL) were significantly higher compared to all the diabetic subjects.

Table-2: Effect of treatment Duration in Diabetes Mellitus on FBG and Lipid profile

Charac Teristics	N	FBG (mmol/L)	TC (mg/dL)	TG (mg/dL)	HDL (mg/dL)	LDL (mg/dL)
Group A1	17	8.71±1.82	186.52 ± 9.51^{beq}	130.82±20.42	60.19±4.83	92.01±6.94
Group A2	19	8.94±1.16	191.53 ± 10.63^{aeq}	122.53±28.31	59.40±4.17	91.00±9.81
Group A3	20	11.37 ± 1.25^{q}	190.69 ± 11.42^{eq}	135.76±30.41	67.53 ± 4.48^{a}	99.07±10.54
Group A4	20	11.00 ± 0.92^{q}	190.91 ± 8.41^{eaq}	170.04 ± 22.38^{a}	64.70 ± 3.30^{a}	104.45±7.75
Group A5	24	10.70 ± 0.65^{q}	191.93 ± 5.94^{abcdq}	193.58 ± 15.83^{a}	57.77 ± 2.33^{abcdq}	113.85±5.48abc
Group C (Control)	100	5.96 ± 0.64^{cde}	178.84 ± 5.82^{abcde}	83.28 ± 15.51^{de}	91.22 ± 2.28^{cd}	82.94±5.37

Values are express as mean ± SEM; Values of the group with superscript "a" are significantly ($p<0.05$) different from group A. Values of the group with superscript "b" are significantly ($p<0.05$) different from group B. Values of the group with superscript "c" are significantly ($p<0.05$) different from group B. Values of the group with superscript "d" are significantly ($p<0.05$) different from group D. Values of the group with superscript "e" are significantly ($p<0.05$) different from group E. Values of the group with superscript "q" are significantly ($p<0.05$) different from group C.

DISCUSSION

Type 2 diabetes mellitus is one of the major non communicable diseases in Nigeria that is associated with vascular disease as a result of abnormal lipid metabolism. Several reports have shown that diabetic patients tend to have higher tendency of developing atherosclerosis compared to non-diabetic patients as a result of dyslipidaemia due to insulin resistance. The result of lipid profile of diabetic subjects living with the diseases for more 5years in this study shows the mean concentration of Total cholesterol (TC), Triglyceride (TG), and Low-Density Lipoprotein (LDL) were significantly higher compared to diabetic subjects with the diseases for less than 5years. This is in agreement with a research carried out in Pakistan by [31], it revealed that duration of diabetes was associated with higher incidence of dyslipidemia, increase in duration of diabetes mellitus could result to more resistance to receptor as a result of aging. Dyslipidaemia is well known risk factors for cardiovascular and renal diseases amongst subjects when compared to control. However, the (HDL), which is cardio-protective was significantly lower compared to control. Dyslipidemia is a metabolic abnormality mostly associated with diabetes mellitus [4]. Derangement in lipid metabolism have been reported in patients with diabetes mellitus accompanied by the risk of cardiovascular arteriosclerosis [3]. In diabetes a lot of factors could affect serum lipid level, due to interrelationship between carbohydrates and lipid metabolism [5]. Consequently, any disorder in

carbohydrate metabolism can result to disorder in lipid metabolism and vice versa [6]. Insulin resistance is a primary defect in the majority of subjects with type II diabetes mellitus [7]. Many studies have shown that insulin affects the liver apolipoprotein production and regulates the enzymatic activity of lipoprotein lipase and cholesterol ester transport protein, which causes dyslipidemia in diabetes. However, insulin deficiency reduces the activity of hepatic lipase and several steps in production of biologically active lipoprotein lipase [9]. Hypertriglyceridaemia usually accompanies fall in HDL cholesterol, which is also a significant feature of plasma lipid abnormalities seen in individuals with diabetes [30], just like in this present study. The result of lipid profile of diabetic subjects with the diseases for more 5years, in this study shows the mean concentration of Total cholesterol (TC), Triglyceride (TG), and Low-Density Lipoprotein (LDL) were significantly higher compared to diabetic subjects with the diseases for less than 5years. This is in agreement with a research carried out in Pakistan by [31], it revealed that duration of diabetes was associated with higher incidence of dyslipidemia.

CONCLUSIONS

This present study revealed that, as the duration of treatment of diabetes mellitus increases, tendency of having abnormal lipid metabolism also increases in Hausa/Fulani.

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