Original Article

Serum Total Adiponectin and its Relationship with Glycemic Control ad Markers of Lipoprotein Metabolism in Nigerians with Type 2 Diabetes Mellitus

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Abstract

Background: Adiponectin is a hormone that is mostly and abundantly produced by the adipocytes and directly sensitizes the body to insulin. Due to the increasing prevalence of Type 2 diabetes mellitus (T2DM) in sub-Saharan Africa, serum adiponectin has attracted much attention because of its anti-diabetic, anti-atherogenic and anti-inflammatory effects. Therefore, the aim of this study was to determine the relationship between serum adiponectin and the metabolic control of plasma glucose and lipids among type 2 diabetic patients. **Methods:** This was a cross-sectional study of Type 2 diabetic adult Nigerian males and females with age and sex-matched non-diabetic controls. Fasting serum total adiponectin, triglyceride (TG), total cholesterol (TC), high-density lipoprotein-cholesterol (HDL-C), low-density lipoprotein-cholesterol (LDL-C), plasma glucose (FPG) and glycated haemoglobin (HbA1C) were determined. Dyslipidemia was defined based on the third report of National Cholesterol Education Programme, Adult Treatment Panel III (NCEPATP III). Statistical analyses were performed using SPSS version 19 and $p<0.05$ was considered to be significant. **Results:** One hundred and eighty subjects (106 females and 74 males) were recruited for the study. Type 2 diabetes mellitus subjects were 110 (61.1%) with mean age of 54.5yrs while healthy non-diabetic controls were 70 (38.9%) with the mean age of 51.8yrs. The prevalence of hypoadiponectinemia T2DM subjects was (82.4%) with a (mean value of 10.71 ± 1.85ng/ml) and 17.6% among the controls (mean value 21.14 ± 1.98ng/ml) after log transformation. The correlation coefficients between serum adiponectin and lipid profile parameters, HbA1C and FPG among the subjects were: TG (r=-0.022, p=0.045), TC (r=- 0.014, p=0.114), HDL-C (r=0.01, p=0.808), LDL-C (r=- 0.007, p=0.267), HbA1C (r=- 0.24, p=0.001), FPG (r=- 0.22, p=0.003). There were weak but significant negative correlations of adiponectin with FPG and HbA1C. There were weak negative correlations between serum adiponectin and the lipid profile parameters except HDL-C. **Conclusion:** Serum adiponectin level was significantly lower among type 2 diabetic Nigerians than their control (non-diabetic) counterparts.

Keywords: Adiponectin; Metabolic control; Type 2 diabetes; Nigeria

Introduction

Type 2 diabetes mellitus (T2DM) is a heterogeneous group of metabolic disorders characterized by variable degrees of insulin resistance, impaired insulin secretion and increased glucose production. [1] Insulin plays a key role in the regulation of intermediary metabolism of glucose and lipids. Thus, impaired insulin action and/or secretion are often associated with abnormal metabolic control with consequent development of dysglycemias and dyslipidemias. [2] The increased incidence and prevalence of T2DM globally has led researchers to work endlessly to unravel the pathogenic mechanisms that underlie T2DM and its comorbidities such as insulin resistance, impaired glycaemic status, and dyslipidemia. [3]

Recently, some adipose tissue-secreted hormones (adipocytokines or adipokines) have been implicated in the pathogenesis of obesity, insulin resistance and T2DM. [4] Chief among the adipocytokines includes leptin, resistin and adiponectin. [5] Adiponectin is a major adipokine with far-reaching effects on glucose and lipid metabolism. It is known to have anti-obesity, antidiabetic, anti-inflammatory and immunomodulatory actions. [6] It has been implicated in the pathogenesis of obesity, insulin resistance and T2DM. Mounting physiological, pathophysiological and genetic evidences strongly implicate adiponectin in the development of T2DM and its complications such as chronic hyperglycemia and dyslipidemias. [7,8] Reduced adiponectin levels are documented in the obesity, insulin resistance and T2DM [9,10] while high adiponectin levels are associated with reduced risk of T2DM. [11] Insulin-sensitizing, anti-diabetic drugs cause an increase in plasma adiponectin levels. [12] Adiponectin maps to a genome locus that is associated with susceptibility to T2DM. [13] In addition several adiponectin gene missense mutations that are associated with T2DM have been described. [14]

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Though many studies have been carried out to investigate the pathogenic role of adiponectin in T2DM among Caucasians, Asians, and African-Americans, there is paucity of similar data in native Africans including Nigerians with T2DM. To bridge the information gap, this study was designed to determine serum adiponectin level and investigate its associations with glycemic control and dyslipidemia in patients with T2DM.

Subjects and Methods

This was a cross-sectional study of adult type 2 diabetics patients attending the Endocrinology Outpatient Clinic of Lagos University Teaching Hospital (LUTH) and a control group recruited from apparently healthy health workers in Lagos University Teaching Hospital. Purposive sampling of consecutive patients that attended the diabetic clinic of LUTH who were already diagnosed with diabetics was carried out. The control groups were apparently healthy adults with normal fasting plasma glucose levels. This study was reviewed and approved by the Research and Ethics Committee in compliance with the Declaration of Helsinki (HREC Number: ADM/DCST/HREC/VOL. XVI/APP/753).

Type 2 diabetic patients aged between 35 and 75 years (who agreed to participate in the study) were recruited. Baseline demographic data were collected from both the study and the control groups. Body weight in kilogram (kg) was measured in the upright position using a portable, digital weighing scale that had been validated with calibrated weighing masses. The height in meters (m) was measured using a standing metre rule affixed to a wall. The body mass index (BMI) was calculated using the formula:

BMI=Weight in kg/(height)^2 in m^2 and expressed in kg/m^2.

Blood pressure (BP) was measured over the left arm (using ACCOSON mercury sphygmomanometer) after 10 minutes of rest, with the subjects in sitting position. Systolic blood pressure (SBP) was taken to correspond to the appearance of Korotkoff sound (phase I) and diastolic blood pressure (DBP) corresponds to the disappearance of Korotkoff sounds (Phase V). Patients being managed for type 1 DM, as well as pregnant women with pre-existing T2DM or gestational DM were excluded. Informed consent was obtained from each study participant. Adequately tested questionnaires were administered for collection of qualitative data and recording of quantitative variables.

The subjects were instructed to fast overnight (between 10 to 12 hours) before sample collection the following morning. On the agreed morning, after antiseptic preparation of the venipuncture site, 8 millilitres of blood (8ml) of venous whole blood was collected and distributed accordingly: three millilitres (3 ml) of venous blood was collected into a plain specimen tube for serum total adiponectin and lipid profile, 3 ml of the blood sample was put into EDTA tube for glycated haemoglobin estimation, 2 ml of blood was introduced into fluoride oxalate tube for fasting plasma glucose estimation. Specimens in the plain bottle were allowed to clot and retract for 30 minutes, then all collected specimen were centrifuged at 3000 rpm for 5 minutes at room temperature. Plasma specimen for glucose were analysed daily but the serum samples were aliquoted into two cryogenic storage tubes (each for serum total adiponectin and lipid profile). Aliquoted specimens were stored for a maximum of two weeks at – 20°C in a well-monitored freezer. Samples for glycated haemoglobin were stored at 4°C and were analyzed weekly.

Glucose oxidase method was used to estimate fasting plasma glucose concentration using a kit produced by Biolabo (R) (Biolabo SA, 02160, Maizy, France) and measured with a spectrophotometer. Ion exchange chromatographic method was used to estimate the levels of glycated haemoglobin using a kit produced by Fortress Diagnostics (R) (Fortress Diagnostics Limited, Unit 2C Antrim Technology Park, Antrim, BT41 1QS, United Kingdom). Enzymatic methods were used to measure the serum lipid profile parameters using kits manufactured by Biolabo (R) (Biolabo SA, 02160, Maizy, France) and were measured with spectrophotometer. A sandwich solid-phase enzyme-linked immunosorbent assay (ELISA) was used to measure serum total adiponectin using ELISA kit produced by Biovendor (R) (Brovendor – Laboratorni Medicina as, Karasek 1767/1, 621, 00 Brno, Zech Republic). The ELISA was read using a Biorad microwell reader (Bio Rad, USA). Both intra-and inter-assay coefficients of variation were <10% using the Biorad microwell reader.

Analytical quality control was performed for the serum lipids, plasma glucose, and glycated haemoglobin assays using biovine precision multisera (levels 2 and 3) from Randox (R) (RANDOX Laboratories Ltd., Ardmore, Diamond Road, Crumlin, Co. Antrim United Kingdom). The ELISA quality control materials, low and high levels manufactured by Biovendor (R) (Brovendor – Laboratorni Medicina as, Karasek 1767/1, 621, 00 Brno, Zech Republic) were used for serum adiponectin.

Statistical analysis of the data was performed using SPSS Software Version 19 (SPSS Inc. Chicago IL, USA) statistical package. The data were tested for normality using Kolmogorov – Smirnov test. Data that were not normally distributed were log – transformed. Pearson correlation coefficient and multiple linear regression analysis were carried out where appropriate. A $p< 0.05$ was considered to be statistically significant.

Results

One hundred and ten (110) subjects (106 female and 74 males with mean ± standard deviation (SD) age of 54.5±11.3 years were recruited for this study while 70 age matched non-type 2 diabetic adults were recruited as control subjects [Figures 1-4].

The mean ± standard deviation (SD) serum total adiponectin in the subjects was 10.7 ± 1.9ng/mL which was significantly lower than that of the control group (21.1 ± 1.0 ng/mL).

The prevalence of hypoadiponectinemia observed among all the type 2 diabetic patients was 82.4% using a cut off of 13.5 ng/mL. [14]

Pearson correlation analyses between serum total adiponectin and lipid profile parameters among all diabetic subjects showed no correlation except with HDL-C (TC: r=0.11, p=0.0114) (LDL-C: r=0.08, p=0.267), (TG: r=0.14, p=0.045), (HDL-C: r=0.808, p=0.01). Glucose (r=-0.22, p=0.003) and glycated haemoglobin (r=-0.24, p=0.001) showed negative correlations with serum total adiponectin.

Table 1 shows association between diabetic status and levels of adiponectin. Majority (82.4%) of the respondents who had low adiponectin level were diabetic, 39.3% of those who had normal levels of adiponectin were diabetic. The difference in proportions between the diabetic group and controls was statistically significant.

The subjects on the average had statistically significant lower values of serum total adiponectin compared to the controls with mean value of 12.96 ng/mL and 27.08 ng/mL respectively. The values in the subjects were lower than overall mean values of all the respondents [Table 2]. The distribution in both subjects and controls were skewed hence the values were log-transformed and compared. The type 2 diabetic subjects had significantly lower serum total adiponectin values than the controls.

The Table 3 shows a weak but significant negative correlation of adiponectin with FPG and HbA1c. However, there was no correlation between adiponectin and lipid profile parameters except HDL-C.

The Table 4 shows the mean values of Age, BMI, weight and height of the study population which consisted of Group A (type 2 DM) and Group B (controls). There were no statistically significant difference between the anthropometric parameters of the type 2 subjects and the control group.

The Table 5 shows the mean values of adiponectin in both the female and male subjects. The mean value of adiponectin in the female subjects (11.38 ± 1.8) was slightly higher than the mean value of adiponectin in the male subjects (9.67 ± 1.8) and it was statistically significant (p=0.001). In the controls, the mean value for the male subjects (21.76 ± 2.0) was higher than that of the female subjects (20.56 ± 1.0), this was statistically significant (p=0.001). All together there was no statistically significant difference in the mean of both sexes among the diabetics and controls.

Classification according to NCEP ATP 111 guidelines

Among the majority of the respondents had desirable total cholesterol levels [Table 6]. However, approximately 75% of the respondents who had either borderline or high risk values were in the diabetic group. This difference in proportion was statistically significant. Similar pattern was repeated with low density lipoprotein and triglycerides where most had desirable values but more than 80% of the respondents

Table 1: Adiponectin among the subjects and control.

	Group A (T2DM) N= 110	Group B (control) N= 70	X^2	p-value
Adiponectin (ng/mL)	**Subjects**	**Controls**		
Abnormal or low	75 (82.4%)	16 (17.6)	**35.15**	**0.001**
Normal	35 (39)	54 (60)		
Total	**110 (61.1)**	**70 (38.9)**		

Table 2: Mean adiponectin levels among the groups.

Variable	All Groups	Group A (T2DM)	Group B (controls)	p-value
Adiponectin (ng/mL)				
Mean ± SD	18.45 ± 16.81	12.96 ± 8.6	27.08 ± 22.14	
Median	14.10	10.20	18.25	
Interquartile range	8.75 - 20.00	7.37 - 16.97	14.57 - 33.82	
Log transformed mean	13.96 ± 2.06	10.71 ± 1.85	21.139 ± 1.98	0.001

Table 3: Pearson correlation coefficient of adiponectin with FPG, HbA1C and lipid profile of the study groups.

Variable correlation	Group A (type 2 DM) R	p-value	Group B (control) R	p-value
FPG (mmol/L)	- 0.22	0.003		
HbAlc (%)	- 0.24	0.001		
TG (mmol/L)	- 0.14	0.045	0.240	0.87
TC (mmol/L)	0.11	0.114	0.252	1.00
HDL-C (mmol/L)	0.01	0.808	0.209	0.10
LDL-C (mmol/L)	0.08	0.267	0.282	0.85

Table 4: Mean of anthropometric parameters of the study population.

Variable	Group A (type 2 DM) Mean ± SD	Group B (controls) Mean ± SD	T	p-value
Age (years)	54.49 ± 11.38	51.76 ± 13.6	1.45	0.148
Weight (Kg)	73.45 ± 5.74	67.39 ± 16.9	2.4	0.016
Height (m)	1.61 ± 0.068	1.98 ± 3.11	1.22	0.223
Body Mass Index (Kg/m^2)	27.96 ± 5.39	27.63 ± 12.4	0.24	0.809

SD: Standard Deviation; T: Independent T Test Statistic

Table 5: The relationship between adeponectin and gender (male and female) in the study population.

Variable	Group A (type 2 DM) Adiponectin		Group B (control) Adiponectin		T	p-value
Gender	**N**	**Mean ± SD**	**N**	**Mean ± SD**		
Male	40	9.67 ± 1.8	34	21.76 ± 2.0	5.0	0.001
Female	70	11.38 ± 1.8	36	20.56 ± 1.9	4.6	0.001

Table 6: Lipid profile of the study population.

Variables	Group A (type 2 DM)	Group B (control)	Total	p-value
TC (mmol/L)				
Desirable	50 (48)	54 (52)	104	0.001
Borderline	27 (73)	10 (27)	37	
High risk	33 (35)	6 (15)	39	
HDL-C (mmol/L)				
Desirable	70 (55)	56 (44)	126	
Borderline	31 (76)	10 (24)	41	0.001
High risk	9 (69)	4 (31)	13	
LDL-C (mmol/L)				
Desirable	49 (54)	42 (46)	91	
Borderline	19 (50)	19 (50)	38	0.001
High risk	42 (82)	9 (18)	51	
TG (mmol/L)				
Desirable	67 (51)	63 (48)	130	
Borderline	23 (88)	3 (12)	26	0.001
High risk	20 (83)	4 (17)	24	

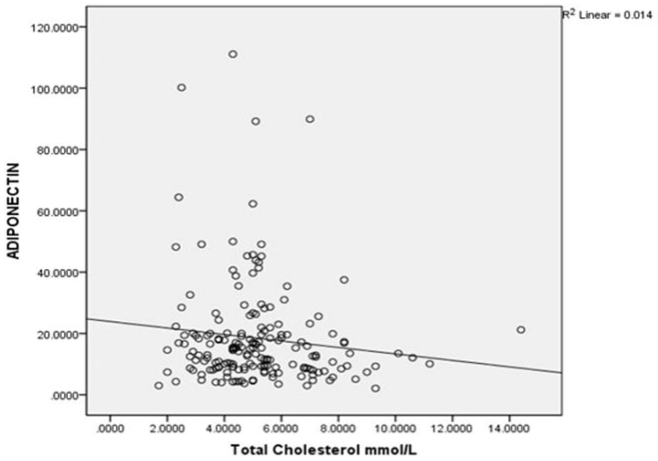

Figure 1: The line shows that total cholesterol is negative correlated with adiponectin but a weak correlation with r^2 of 0.014.

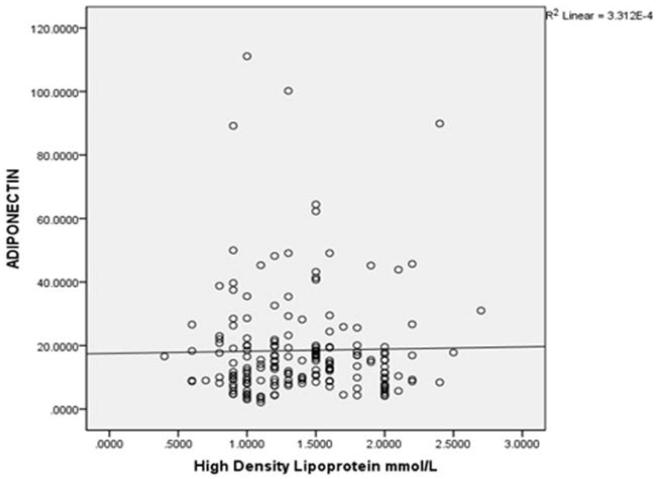

Figure 2: The graph shows linear regression of adiponectin against high density lipoprotein cholesterol. The line is horizontal which means there was no correlation between adiponectin and HDL C.

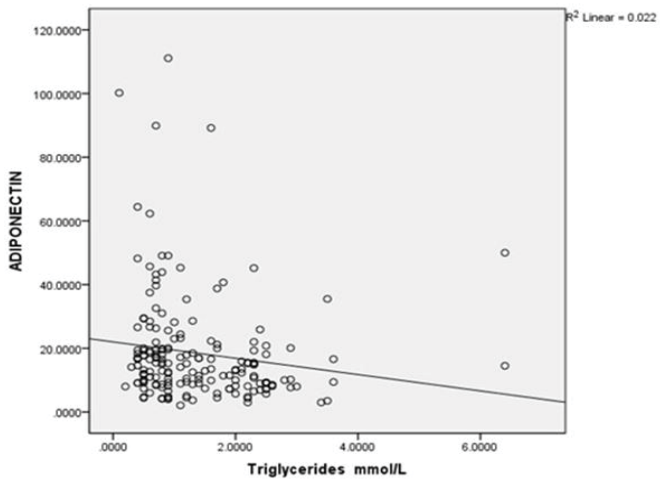

Figure 3: The graph shows linear regression of adiponectin against triglycerides. The line shows that triglyceride is negatively correlated with r^2 of 0.022.

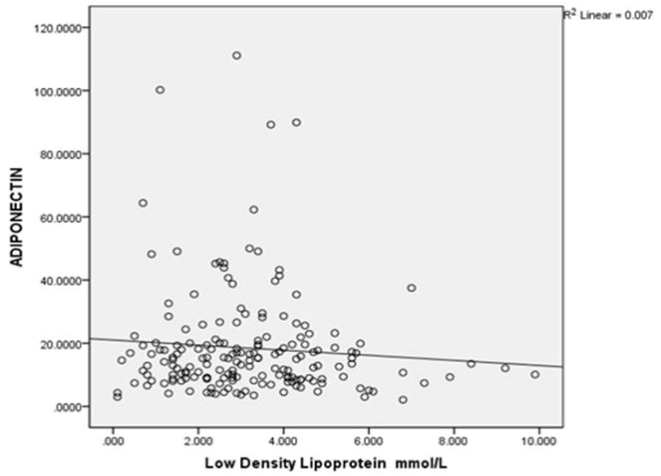

Figure 4: The graph shows linear regression of adiponectin against low density lipoprotein cholesterol. The line is almost horizontal which means there was no correlation between adiponectin and LDL C.

with high risk values were diabetic. However, with respect to high density lipoprotein although majority had desirable values while similar proportions of respondents in both diabetics and controls had high risk or borderline values.

Discussion

Adiponectin, a 244 amino acid protein with a molecular weight of approximately 30KDa is predominantly produced by the adipose tissue [7,15] It belongs to the soluble defence collagen super family of proteins. [15] Structurally, it has a collegen-like and complement factor C1q-like globular domain. [15] Adiponectin is secreted in relatively large amounts into the circulation by the adipose tissue. It is abundantly present in the circulation where it makes up approximately 0.01% of total plasma protein concentration. [7] Plasma levels of adiponectin tend to decrease in insulin resistant states such as obesity, metabolic syndrome, and T2DM.10

In agreement with previous reports, our study demonstrated significant reduction of serum adiponectin in subjects with T2DM when compared with those of the control group. The reduction of serum adiponectin in T2DM patients was independent of their body mass indices. The difference between serum adiponectin levels in T2DM patients and the control group has been attributed to underlying insulin resistance among types 2 diabetic patients. [16] Usually, insulin regulates the secretion of various proteins from adipose tissue including adponectin. Adiponectin promotes insulin sensitivity and inhibits insulin resistance. [17,18] Thus, decreased adiponectin levels in patients with T2DM may be explained by the presence of prevailing insulin resistance. However, the cause-and-effect relationship between hypoadiponectinemia and insulin resistance is not fully clear. For the control group in this study, they had higher serum adiponectin concentrations when compared with T2DM patients. In addition, they showed lower prevalence of insulin resistance. Adponectin essentially has an antidiabetic and hypoglycaemic effect. [19] It has been reported to activate hepatic insulin receptor and promote pancreatic beta-cell function. [20] Therefore decreased circulating adiponectin concentrations in patients with T2DM would enhance underlying insulin resistance and beta-cell dysfunction which are pathogenetic hallmarks of T2DM. Adiponectin also modulates the interaction between skeletal muscle and hepatic insulin receptors by activation of 5 adenosine monophosphate-activated protein kinase (AMPK) pathway. [21] This potentiates the antidiabetic and glucose lowering effect of adiponectin. Other potential mechanisms for the glucose-lowering effect of adiponectin include; suppression of hepatic glyconeogenesis, stimulation of fatty acid oxidation in the liver; stimulation of glucose uptake and fatty acid oxidation in skeletal muscle and stimulation of insulin secretion from pancreatic beta-cells. [6,7] These effects may be partly mediated by stimulatory effects of adiponectin on the AMPK as well as peroxisome proliferator-activator-receptor-gamma (PAPR-ϒ) signalling pathways. [21,22]

Some previous studies have reported sexual dimorphism of circulating adiponectin concentrations in both children and adults. [23] In our study, there was no sex difference in serum adiponectin concentrations among the subjects. Commonly, circulating adiponectin concentration is said to be higher in females than in males, possibly due to influence of sex hormones. Androgens tend to decrease plasma adiponectin concentration while estrogens have no effect. [24,25] The reason for non-demontration of sexual dimorphism in our study may be due to the skewed nature of the female participants. Most female subjects that participated in the study were postmenopausal. The adiponectin-increasing effect of female sex hormones (estrogens) may not be optimal in this category of women and this could abolish the gender-associated differences in serum adiponectin levels in the study subjects. In postmenopausal women, estrogen replacement has been shown to reduce plasma adiponectins. [26]

This study showed that the serum lipid profile of type 2 diabetic patients were borderline high in contradistinction of those of the control group whose lipid profile were mostly within desirable values. This is in tandem with the well-known association of dyslipidemia with type 2 diabetes. [27] Therewere varying correlations between adiponectin and the serum lipid profile parameters in the type 2 diabetic subjects. First, there is a negative correlation between serum TG concentration and adiponectin in the type 2 diabetic subjects. This is in line with the findings of a similar study report by and Co-workers. [28] Hypertriglyceridemia is a common form of atherogenic dyslipidaemia. [27] Its presence in type 2 diabetic patients may not be unconnected with the prevailing hypoadiponectinemia. The inverse relationship between serum triglyceride and adiponectin concentrations have been explained by the hypothesis that adiponectin may increase the production and activation of lipoprotein lipase and the expression of VLDL receptors. [29] This will reduce the storage of triglycerides in adipose tissue and their uptake by the hepatocytes. The overall effect will be increased circulating concentration of triglyceride (hypertriglyceridemia). Furthermore, hypertriglyceridemia is a major component of the metabolic syndrome which is also characterized by hypoadiponectinemia. [30]

There was positive correlation between serum adiponectin and HDL-C concentrations in this study. This is in line with the findings by similar studies that reported positive correlation between HDL-C and adiponectin that was independent of BMI and insulin resistance in type

2 diabetic patients. [31] In contrast, there was no correlation between serum adiponectin and LDL-C and TC in both type 2 diabetic subject and the control group. A similar study conducted in Japan showed a negative correlation between LDL-C, TC, and serum adiponectin concentration in type 2 diabetics. [32] The negative correlation was explained to be likely due to prevailing hypoadiponectinemia which is associated with reduced activation of peroxisome proliferator – activator receptor-alpha (PPAR-α) receptors in the liver as well as decreased expression of LDL receptors in body tissues. [32] The reason for the presence of no correlation in our study could not be pathophysiologically explained. However, differences in sample size, ethnicity, and diet may be responsible. [33] Our study has two obvious limitations: the cross-sectional design, relatively small sample size, and potential influence of confounding factors such as patient's medications and associated co-morbidities. Hence, cause-and-effect relationships cannot be established between serum adiponectin and its covariates in the study subjects. In addition, the skewed gender distribution of the study participants had already been mentioned above. Furthermore, comparison of all results with similar local studies was not possible due to limited literature on serum adiponectin and its association with clinical and metabolic parameters in type 2 diabetic Nigerians. Further studies with a larger sample size and well-controlled confounding factors may be needed to substantiate our present findings.

Conclusion

The findings of this study to some extent is in support of the hypothesis that decreased circulating adiponectin levels contributes to dysglycemia and dyslipidemia which are the hallmarks of poor metabolic control patients with T2DM. More studies on the role of adiponectin on the pathogenesis and complications of T2DM are recommended among Nigerians afflicted with this common metabolic decrease.

Conflict of Interest

The authors disclose that they have no conflicts of interest.

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