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Original Research Article

Hypercortisolaemia and dyslipidaemia in a selected diabetic population

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Abstract

Background: Type II DM and obesity are metabolic disorders characterized by insulin resistance, dyslipidaemia, and metabolic stress. These features were assessed in patients using fasting plasma glucose, fasting lipid profile and serum cortisol as their markers.

Materials and methods: Ninety participants were recruited and classified into 3 groups of thirty each – Obese with type II DM, Non-obese with type II DM, non-obese and non-diabetics who served as controls. Anthropometric measures of weight and height were taken using standard procedures and body mass index was calculated thereafter. Blood samples were collected after an overnight fast for the in vitro assay of serum cortisol, plasma glucose, triglycerides, total cholesterol, low density lipoprotein cholesterol and high density lipoprotein cholesterol using enzyme linked immunosorbent assay and colorimetry as appropriate. Data obtained were analyzed statistically using ANOVA and *post hoc* test for comparison of variables between groups. Pearson's correlation was performed to assess the relationship between variables and $p<0.05$ was considered significant.

Results: Serum cortisol, plasma glucose, total cholesterol, triglycerides and LDL-cholesterol were elevated while HDL-cholesterol was reduced in both obese and non-obese subjects with type II diabetes mellitus when compared with controls. Cortisol had a significant positive association with plasma glucose, total cholesterol, triglycerides and LDL-cholesterol in obese subjects with type II diabetes mellitus while cortisol had a significant inverse relationship with HDL-cholesterol in both obese and non-obese subjects with type II diabetes mellitus.

Conclusion: From this study, we conclude that elevated serum cortisol, a consequence of type II DM, accompanies dyslipidaemia in both obese and non-obese type II DM patients. It could therefore be inferred that 'diabetic stress' is the underlying factor of elevated cortisol in this group.

Keywords: Cortisol, Dyslipidaemia, Insulin resistance, Obesity, Diabetes mellitus.

1. Introduction

Diabetes mellitus (DM) is a group of metabolic diseases characterized by hyperglycemia resulting from defective insulin secretion (Type I), insulin action (Type II), or both [1]. Type II DM is also known as non-insulin dependent diabetes mellitus or adult-onset diabetes mellitus. Occurring mostly in adults, it accounts for up to 90% of all cases of diabetes. Type II DM is specifically characterized by insulin resistance as well as hyperglycaemia [2], both of which have been implicated in the pathogenesis of diabetic dyslipidaemia.

Insulin resistance as well as hyperglycaemia are both hallmarks of Type II DM [3], and have also been featured in the pathogenesis of diabetic dyslipidaemia, which is characterized by low level of high density lipoprotein cholesterol (HDL-C), associated with defective lipoprotein lipase (LPL) catabolism of triglycerides (TG)-rich lipoproteins, high level of triglycerides (TG), and

postprandial lipemia [4]. The role of insulin resistance has been reviewed extensively [5-8], while hyperglycaemia seems to cause raised levels of atherogenic cholesterol-enriched apolipoprotein B-containing remnant particles by reducing expression of the heparin sulphate proteoglycan perlecan on hepatocytes [9].

Obesity is associated with numerous medical problems, including type II (maturity-onset) diabetes mellitus, hyperlipidemia, insulin resistance and thus hyperinsulinemia [10]. Hyperinsulinemia may aggravate obesity by promoting lipogenesis and inhibiting lipolysis. Prolonged hyperinsulinemia in obesity might lead to the exhaustion of Beta-cells in those individuals who are genetically susceptible to diabetes mellitus [11].

Cortisol plays counter-regulatory role in glucose metabolism. It is a hormone whose level increases due to stress, mostly biological stress. Increased levels of cortisol, the main stress hormone, may come as a result of biological stress induced by diabetes but can also induce hyperglycemia, as well as hyperlipidemia [12,13]. In Type II DM, cortisol secretion has been suggested to be a possible link between insulin resistance and obesity/dyslipidaemia [14].

Although, cortisol directly plays a role in glucose metabolism involving insulin, the particular mechanism explaining the role of cortisol in the development of obesity remains unclear. So far, a direct relationship between diabetes and cortisol concentration in obese and non-obese individuals remains to be established, as there have been inconsistencies in the studies conducted so far. Previous studies have reported a relationship between levels of glucose and cortisol in obese individuals. There is however paucity of data on the relationship between cortisol and lipid profile in obese and non-obese Nigerian adults with Type II DM. This study is therefore designed to assess the relationship between serum cortisol, and fasting lipid profile in obese and non-obese individuals with Type II DM.

2. Materials and Methods

This cross sectional study was carried out in a specialist hospital located in the south-western region of Nigeria, between January and July 2017. A total of ninety (90) participants were recruited into the study, they comprise of thirty (30) overweight/obese subjects with type II DM (ODM), thirty (30) non-obese subjects with type II DM (NODM), as well as thirty (30) apparently healthy subjects who were non-diabetic and non-obese, serving as controls. All type II DM subjects were newly diagnosed and all the participants were drug naïve.

A semi structured questionnaire was administered to obtain basic demographic data, information on smoking habits, alcohol, drug and medication use. Body weight in kilogram (kg) was measured using a standard weighing scale and height (m) was measured using a stadiometer. Body mass index was calculated as the ratio of body weight (kg) to the square of height (m^2).

World Health Organization (WHO) body mass index (BMI) classification [15] was used and participants whose BMI was above 25kg/m^2 were classified as overweight, while participants with BMI between 18.0 and 24.9kg/m^2 were classified as non-obese. The cut-off level of fasting blood glucose for type II diabetes mellitus was 110mg/dL.

This study excluded children, pregnant women, individuals that take alcohol, individuals that smoke, individuals with HIV, individuals with hepatitis, and individuals that have other known chronic medical conditions such as hypertension. Underweight individuals i.e. individuals with BMI <18kg/m^2, and those unwilling to give their consent were also excluded from the study.

Informed consents were obtained from each participant and ethical clearance was obtained from Babcock University Health and Research Ethics Committee (BUHREC).

2.1 Sample collection

Subjects were required to undergo an overnight fast which lasted about 10 – 12 hours to end at 0800 hours on the day of sample collection. Six millilitres (6mL) of venous blood was collected and dispensed as follows: 4mL into plain bottle and 2mL into fluoride oxalate bottle. The samples were centrifuged, and separated within one hour of sample collection to extract the serum/plasma. Plasma obtained from fluoride oxalate bottle was used to analyze for glucose, while serum obtained from the plain bottle was used to analyze for cortisol and lipid profile.

2.2 Analytical methods

Plasma glucose was determined by the glucose oxidase method using reagents supplied by Randox Laboratories Ltd. (UK) as previously described by Ojiako *et al* [16]. Plasma total cholesterol (TC), triglyceride (TG) were determined using standard enzymatic methods using reagents supplied by Randox Laboratories Ltd. (UK) as previously described by Ojiako *et al* [16]. High density lipoprotein-cholesterol (HDL-c) was determined by a two-step procedure using a precipitant to isolate non-HDL-c component in the plasma and this is followed by quantitative determination of HDL-c by standard enzymatic method for cholesterol determination (Randox Laboratories Ltd., UK). LDL cholesterol was determined using Friedwald equation [17], while serum cortisol was determined using ELISA (GenWay Biotech Inc., USA)

2.3 Statistical analysis

Data generated from this study were analyzed using the statistical package for social sciences (SPSS 17th edition) computer software. Comparison of variables between groups was done using one-way analysis of variance (ANOVA) followed by a *post-hoc* test. Pearson's

correlation was used to test the association between variables. The significant threshold was fixed at P<0.05. The results were expressed as mean ± standard deviations and presented in tables.

3. Results

Table 1 shows the anthropometric and biochemical data of the study participants recruited. NODM and controls had comparable BMI, while ODM had higher BMI than NODM as well as controls. There were significant differences in the BMI, plasma levels of glucose, serum levels of triglyceride, total cholesterol, low density lipoprotein cholesterol (LDL-C), and HDL-C (P<0.05) between the study and control subjects.

Furthermore, the mean BMI for obese subjects with type II DM is significantly different from both non-obese type II DM and control subjects (p<0.05). The glucose levels in obese subjects are significantly higher when compared with non-obese and control subjects (p<0.05), also the glucose levels in non-obese subjects are statistically different from controls.

Moreover, the serum levels of triglyceride, total cholesterol, LDL-C, and HDL-C in both obese and non-obese subjects with type II DM are significantly different from controls. There was significant statistical difference in the serum levels of cortisol in both obese and non-obese type II DM subjects when compared with control subjects, however, there was no significant statistical difference between obese and non-obese subjects.

Table 2 shows the correlation between cortisol, anthropometric and biochemical parameters in obese subjects. There was significant positive correlation between cortisol and glucose levels and triglyceride, total cholesterol, and LDL-C (P<0.05). There was negative correlation between cortisol values and HDL-C (P<0.05). There was no significant correlation between cortisol and BMI.

Table 3 shows the correlation between cortisol and type II diabetes in non-obese study subjects. There was significant positive correlation between cortisol and glucose levels and triglyceride, total cholesterol, and LDL-C (P<0.05). There was negative correlation between cortisol values and HDL-C (P<0.05). There was no significant correlation between cortisol, and BMI.

Table 1: Anthropometric and biochemical data of the study participants recruited (Mean ± standard deviation (S.D))

	ODM (n = 30)	NODM (n = 30)	Control (n = 30)	F	p value
BMI (kg/m^2)	34.743±5.0643^{a,c}	23.150±1.4771^{b}	21.410±2.0116^{b}	148.334	0.000*
Glucose (mg/dl)	119.27±42.405^{a,c}	153.60±51.474^{a,b}	85.73±10.680^{b,c}	22.718	0.000*
Cortisol	151.00±107.421^{a}	153.63±157.171^{a}	119.43±59.753^{b,c}	22.718	0.04*
Cholesterol	212.40±40.537^{a}	182.87±63.695^{a}	168.17±53.741^{b,c}	4.582	0.04*
Triglycerides	99.47±61.683^{a}	93.57±65.290^{a}	64.97±33.942^{b,c}	3.324	0.04*
HDL-C (mg/dl)	46.47±21.773^{a}	43.47±25.713^{a}	55.13±16.349^{b,c}	3.282	0.04*
LDL-C (mg/dl)	136.90±40.920^{a}	120.63±56.688^{a}	106.97±62.518^{b,c}	3.152	0.03*

Results are expressed in mean ± standard deviation. *Significant at P<0.05.
a= significantly different from control
b= significantly different from ODM
c= significantly different from NODM

Table 2: Correlation between cortisol, anthropometric and other biochemical parameters in ODM

Cortisol	r-value	p-value
BMI	-0.297	0.11
Glucose	0.372	0.04*
Triglyceride	0.701	0.04*
Total Cholesterol	0.701	0.03*
HDL-C	-0.999	0.000*
LDL-C	0.304	0.02*

Table 3: Correlation between cortisol, anthropometric and other biochemical parameters in NODM

Cortisol	r-value	*P*
BMI	-0.116	0.54
Glucose	0.368	0.04*
Triglycerides	0.132	0.37
Total cholesterol	0.229	0.04*
HDL-cholesterol	-0.515	0.000*
LDL-cholesterol	0.184	0.030*

4. Discussion

Diabetes mellitus (DM) is a metabolic disease characterized by an inability to maintain normal glucose homeostasis that results from an alteration of the secretion or action of insulin, the hormone responsible for the uptake of glucose in the body [18]. Insulin resistance has been reported to be the underlying factor in most of the metabolic consequences of Type II DM.

In this study, we observed that ODM and NODM participants had higher plasma triglyceride, total cholesterol and LDL-C; and lower HDL-C compared with controls. These findings are consistent with features of diabetic dyslipidaemia as reported by Chehade *et al* [19]. These could be attributed to the fact that dyslipidaemia is associated with Type II DM. It has been reported that dyslipidaemia associated with Type II DM is characterised by moderately increased triglyceride levels, carried in very-low-density lipoprotein (VLDL) particles, reduced high-density lipoprotein cholesterol (HDL-C) levels carried in small HDL particles [20-23]. We also observed that there were no significant differences in lipid parameters between ODM compared with NODM. This suggests that Type II DM was enough to cause dyslipidaemia in them, with or without obesity. This emphasizes the role of insulin resistance as the underlying factor in dyslipidaemia.

We also observed higher serum cortisol in diabetic (ODM and NODM) participants compared with controls, while there was no difference in serum cortisol of ODM compared with NODM. This corroborates the fact that elevated cortisol level is associated with Type II DM, and that being obese may not have additional effect on serum cortisol levels. Previous studies have suggested that cortisol secretion is a possible link between insulin resistance and Type II DM [10, 24-26]; therefore our findings of increased cortisol in ODM and NODM compared with controls might as well be responsible for the observed features of dyslipidaemia. Some studies have documented higher plasma cortisol in patients with insulin resistance [27-29]. However the relationship between different insulin resistance (IR) components and serum cortisol is not consistent. In ODM and NODM, we did not observe any correlation between serum cortisol and BMI, suggesting that serum cortisol in Type II DM is not associated with being obese or not. However, we observed a significant positive correlation between serum cortisol and glucose, triglycerides, total cholesterol, LDL cholesterol in ODM; and a significant negative correlation between serum cortisol and HDL cholesterol in them. Similarly, we observed a significant positive correlation between serum cortisol and glucose, total cholesterol and LDL cholesterol in NODM, while HDL has a negative correlation with serum cortisol in NODM. Our finding of a significant negative correlation between cortisol and HDL-C in ODM and NODM might be because high serum cortisol level alters peripheral cholesterol metabolism, thus impaired formation of HDL-C

Furthermore, this study revealed that there is a negative correlation between cortisol and HDL-C in both obese and non-obese subjects with type II DM. This is in agreement with the study done by Fraser *et al* [30]. This is because high levels of cortisol may alter the metabolism of peripheral cholesterol and thus the formation of HDL-C becomes altered.

5. Conclusion

From this study, we conclude that elevated serum cortisol, a consequence of Type II DM, accompanies dyslipidaemia in both obese and non-obese Type II DM patients. It could therefore be inferred that 'diabetic stress' is the underlying factor of elevated cortisol in this group.

Consent

All authors declare that 'written informed consent was obtained from the participants enlisted for this study'. A copy of the written consent is available for review by the Editorial office/Chief Editor/Editorial Board members of this journal.

Ethical approval

All authors hereby declare that all experiments have been examined and approved by the Babcock University Ethics Committee (BUHREC) and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

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