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Evaluation of diagnostic performance of serum copeptin in correlation with dyslipidemia in Obesed and Non-Obesed type 2 diabetes mellitus (T2DM)

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Abstract: *Background:* High fat in the diet is the main explanations for insulin resistance which will cause type 2 DM (T2DM). Obesity has been known to be related to dyslipidemia which may be a metabolic abnormality resulting in a persistent increase within the plasma concentration of cholesterol and triglycerides. This study thus aimed in determining the diagnostic role of copeptin and its association with dyslipidemia in obesed and non obesed diabetic subjects. *Methods:* This research was administered on 50 diabetic subjects and 30 age and sex-matched controls. 5ml of blood was collected from each subject and dispensed into an appropriate anticoagulant bottle. Copeptin and atherogenic indices (Total cholesterol, triglycerides, high density lipoprotein, and low density lipoprotein) were determined using standard laboratory techniques. Statistical analysis of the data was done appropriately and P values less than 0.05 were considered significant. *Results:* The mean values of copeptin, Total Cholesterol, High Density Lipoprotein, and Low Density Lipoprotein were significantly higher in both Obesed and non-obesed diabetic subjects in comparison to the control group ($p<0.05$). Also, FBS had a higher area under the ROC curve (AUROC) than copeptin. *Conclusion:* This study shows that diabetic subjects have higher levels of copeptin and atherogenic indices when it's compared with non-diabetic groups. This actually confirmed that copeptin is related to dyslipidemia which is one among an indicator for top risk of atherogenicity, especially in obesed diabetic subjects that had higher copeptin levels than non-obesed diabetes. Also, copeptin wasn't found to be a more accurate marker of diagnosis for DM when its diagnostic performance with fasting blood glucose decided.

Keywords: Atherogenicity, Copeptin, Dyslipidemia, hyperglycemia, Obesity.

Introduction

Obesity is a medical condition in which excess body fat accumulates to the extent that it may harm health, leading to reduced life expectancy and it is a complex, multi-factorial chronic disease [1]. It has been documented to be associated with many diseases, particularly heart disease, type 2 diabetes, breathing difficulties during sleep, certain types of cancer, and osteoarthritis. The prevalence of obesity is rising to epidemic proportions at an alarming rate in both developed and less developed countries around the world [2]. There is enough evidence indicating a high-fat diet as the major cause of obesity and insulin resistance. Obesity is known to be associated with dyslipidemia, which is a metabolic abnormality leading to a persistent increase in the plasma concentration of cholesterol and triglyceride [3-4].

Clinical features associated with dyslipidemia include hypertriglyceridemia, reduced HDL cholesterol and increased numbers of small dense LDL particles [5]. Elevated LDL cholesterol is not a feature of dyslipidemia seen with abdominal obesity. Other features of the dyslipidemia of abdominal adiposity include elevated very low density lipoproteins (VLDL), and reduced HDL, which are the large buoyant antiatherogenic subspecies of

total HDL. In some individuals, Apo lipoprotein B levels may be elevated, reflecting an increase in the number of small, dense lipoprotein particles (VLDL and LDL) [6]. The Body mass index (BMI; in kg/m2) is widely used for the classification of overweight and obesity in men and women [7-8].

Diabetes mellitus is a group of metabolic disorders characterized by a chronic hyperglycemic condition resulting from defects in insulin secretion, insulin action or both. The autoimmune destruction of pancreatic beta cells leads to a deficiency of insulin secretion which results in the metabolic derangements associated with type 1 diabetes mellitus. In addition to the loss of insulin secretion, the function of pancreatic alpha cells is also abnormal and there is excessive secretion of glucagon [9-10]. Although insulin deficiency is the primary defect in type 1 diabetes mellitus, there is also a defect in the administration of insulin leading to uncontrolled lipolysis and elevated levels of free fatty acids in plasma which suppresses glucose metabolism in peripheral tissues such as skeletal muscles [11-12]. In type 2 diabetes mellitus, there is impaired insulin secretion through a dysfunction of the pancreatic beta cell and impaired insulin action through insulin resistance [13].

Copeptin, which was described for the first time by Holwerda in 1972 [14], is a glycosylated 39-amino acid long peptide with a leucine-rich core segment. It is a cleavage product of the C-terminal part of the arginine vasopressin (AVP) precursor that is produced in equimolar amounts with AVP, a process similar to the generation of insulin and C-peptide. In contrast to AVP, Copeptin is stable both in serum and plasma at room temperature, has a long half-life, and is not bound to platelets [15-16]. It can be easily measured ex vivo as a "shadow" fragment of AVP in the circulation in manual or fully automated chemiluminescence assays. Copeptin is, therefore, routinely used as a surrogate marker for AVP [17].

Arginine vasopressin, which is also named antidiuretic hormone, is released from the posterior pituitary gland in conditions of chronic psychosocial stress via inducing the hypothalamic pituitary adrenal (HPA) axis along with corticotropin-releasing hormone [18]. Copeptin is a C-terminal portion of the precursor of Arginine vasopressin (AVP). Therefore it is considered to be a reliable and clinically useful surrogate marker for AVP [19]. Bjorntorp and Rosmond [20] suggest that stress-mediated activation of the HPA axis may have a role in the pathogenesis of insulin resistance and metabolic syndrome. Although controversy exists over the role of stress in the pathophysiology of type 2 diabetes mellitus. The association of stress with diabetes is not fully understood, owing to differences in study designs and informs and ascertainment of stress as described by Joseph and Golden [21].

In recent years, there are reports published on the use of Copeptin as a biomarker either as a risk factor or a prognostic factor in various clinical conditions such as myocardial infarction (MI), primary hypertension, stroke, acute coronary syndrome, pituitary functioning, Diabetes mellitus (DM), insulin resistance, metabolic syndrome [22]. Dyslipidemia has been noted to play an integral role in the pathogenesis and progression of micro and macrovascular complications in diabetes mellitus patients.

There is enough evidence indicating a high-fat diet as the major cause of obesity and insulin resistance. Obesity is known to be associated with dyslipidemia, which is a metabolic abnormality leading to a persistent increase in the plasma concentration of cholesterol and triglyceride [5]. In type 2 diabetic subjects, hypothalamic-pituitary-adrenal activity is documented to be enhanced in subjects with diabetes complications and the degree of cortisol secretion was correlated with the presence and number of diabetes complications [10, 23]. Therefore this study would be focused on the relationship between copeptin and dyslipidemia in obesed and non-obesed subjects with type 2 Diabetes Mellitus.

Material and Methods

Study Design: This is a case-control study. The research was conducted between January to August 2019. After informed consent from each participant and ethical approval from the Federal Medical Centre Owo Ethics

Committee, a total number of 80 subjects comprising 50 diabetic subjects and 30 age and sex-matched controls were recruited into this study. All the participants were between ages 30-70 years. The diabetic subjects were recruited from Owo metropolis while the control group was apparently healthy individuals who are non-diabetic. Diabetes during this study was defined as supported laboratory findings as fasting plasma glucose levels greater than 7.0mmo/L on two or more occasions [24]. The medical record and private data were obtained via a comprehensive questionnaire after due approval from the ethical committee of the hospital.

Consent and Ethical Approval: Subjects participating during this study were fully briefed on the research protocols within the clinic after which they were required to sign a written consent. Ethical approval for the study was obtained from the Federal Medical Centre, Owo ethical review committee with registration number FMC/OW/380/VOL. LXX/66.

Inclusion Criteria: Diabetic (obesed and non-obesed) subjects, between 30 and 70 years of age and of both genders were recruited for the study. The control group was apparently healthy individuals of both genders with non-diabetes, aged between 30 to 70 years old.

Exclusion Criteria: Subjects with established complications such as hypertension, Human immunodeficiency virus (HIV), hepatitis and cancer; subjects outside the age range of 30 and 70 years, pregnant and breastfeeding mothers were all excluded from the study. The exclusion criteria for the controls were also the same as for subjects.

Sampling Technique and Storage of Sample: Six milliliters (6ml) of venous blood was aseptically obtained from the Median-cubital vein after 12 hours fast. Three (3ml) of venous blood was dispensed into a fluoride oxalate bottle and gently mixed by inverting the container several times for the determination of Fasting blood sugar to confirm diabetic condition. Similarly, 3ml of venous blood was dispensed into a plain bottle for determination of total cholesterol, triglycerides, high density lipoprotein, and low density lipoprotein to confirm dyslipidemia and copeptin. Serum was separated from the plain tubes after retraction by centrifugation for 5 mins at 1792 g, into plain bottles and stored at -20^0 Celsius until the time of analysis.

Analytical Methods: Plasma fasting blood glucose was determined by the glucose oxidase method using reagents supplied by Randox Laboratories Ltd. (UK) as described by Chessbrough [25]. Serum total cholesterol (TC), triglyceride (TG) and High density lipoprotein-cholesterol (HDL-C) were determined using standard enzymatic methods using reagents supplied by Randox Laboratories Ltd. (UK) as previously described by Adediji *et al*. [10]. LDL cholesterol was determined using the Friedwald equation [26]. Serum copeptin was determined using ELISA kits obtained from Melsin Medical Company, USA.

For all participants, height (m) was taken employing a Stadiometer while weight (kg) was measured using a bodyweight weighing scale with the subject wearing light clothing and without shoes. Body Mass Index (BMI) was calculated as the ratio of weight (kg) to the square of height (m2).

Statistical Analysis: A statistical package for social sciences (SPSS) 23.0 version was used for the analysis of the data appropriately. One way analysis of variance (ANOVA) was used for comparison within the groups. Spearman correlation was used to test the association between variables. Data were presented using mean ± standard deviation (mean ± SD) for all quantitative values. A graphical plot of sensitivity (Receiver Operating Curve, ROC) was done and area under ROC (AUROC) of each marker (Copeptin and FBS) was compared using pair-wise comparison. The level of significance was taken as a 95% confidence interval and P values less than 0.05 ($\leq$0.05) was considered significant.

Results

A total number of 80 subjects comprising 50 diabetic subjects with mean age (55.09±8.92) years and 30 control group with mean age (54.00±10.20) years were studied. In table 1, there was a significant difference in the mean values of BMI, FBS, copeptin, TChol, HDL and LDL among obesed diabetic subjects,

non-obesed diabetic subjects and control group ($p<0.05$). Posthoc statistical analysis shows significantly higher mean values of BMI, FBS, copeptin, TChol, HDL and LDL, but the lower mean value of LDL:HDL in both obesed and non-obesed diabetic subjects in comparison to the control group ($p<0.05$). Similarly, the mean values of BMI, FBS, copeptin, TChol, HDL and LDL were significantly higher in both naïve and diabetic subjects under treatment in comparison with the control group ($p<0.05$). So also, the mean levels of BMI, FBS, copeptin, TChol, HDL and LDL were significantly higher in naïve diabetic groups in comparison with diabetic subjects under treatment group ($p<0.05$) (Table 2).

Table-1: BMI, FBS, Copeptin and atherogenic indices in both obesed diabetic, Non-obesed diabetic and non-diabetic subjects

	Obesed Diabetic subjects (n=26)	Non-obesed diabetic subjects (n=24)	Non-diabetic subjects (n=30)	P-Value
BMI (Kg/m^2)	32.73±2.10 [a,c]	25.10±2.50 [c]	24.72±2.54 [b]	0.000*
FBS (mmol/L)	9.93±2.49 [a]	9.50±1.69 [a]	3.39±0.70 [b,c]	0.000*
Copeptin (pmol/L)	7.81±1.12 [a,c]	6.71±1.50 [a,b]	4.58±1.29 [b,c]	0.000*
TChol (mmol/L)	6.25±1.25 [a,c]	4.80±1.13 [a,b]	4.12±0.94 [b,c]	0.000*
TAG (mmol/L)	2.75±0.55 [a,c]	1.75±0.56 [a,b]	1.33±067 [b,c]	0.000*
HDL (mmol/L)	1.77±0.46 [a,c]	1.32±0.49 [a,b]	1.00±0.26 [b,c]	0.000*
LDL (mmol/L)	3.54±0.85 [a,c]	2.55±0.60 [b]	2.52±0.57 [b]	0.000*
Tchol:HDL	4.02±1.85	3.77±0.95	4.22±0.71	0.363
LDL:HDL	2.25±1.49	2.10±0.72 [a]	2.62±0.65 [c]	0.119

* significant at $p\leq0.05$

a = significantly different from control, b = significantly different from Obesed diabetic group, c = significantly different from Non-obesed diabetic group

Key: n=sample size, BMI= Body mass Index, FBS= Fasting blood sugar, TChol= Total Cholesterol, TAG=Triglycerides, HDL= High Density Lipoprotein, LDL= Low Density Lipoprotein

Table-2: Comparison of antherogenic indices, FBS, Copeptin and body mass index in diabetic subjects (Naïve and DM subjects under treatment) and non-diabetic subjects (Control)

	Naive Diabetic subjects (n=22)	DM under treatment (n=28)	Non-diabetic subjects (n=30)	P-Value
BMI (Kg/m^2)	30.79±3.78 [a,c]	24.93±2.74 [b]	24.72±2.54 [b]	0.000*
FBS (mmol/L)	9.83±2.19 [a]	9.74±1.88 [a]	3.39±0.70 [b,c]	0.000*
Copeptin (pmol/L)	7.73±1.09 [a,c]	6.43±1.54 [a,b]	4.58±1.29 [b,c]	0.000*
TChol (mmol/L)	5.73±1.41 [a,c]	4.95±1.22 [a,b]	4.12±0.94 [b,c]	0.000*
TAG (mmol/L)	2.47±0.74 [a,c]	1.76±0.54 [a,b]	1.33±0.67 [b,c]	0.000*
HDL (mmol/L)	1.61±0.49 [a]	1.37±0.54 [a]	1.00±0.26 [b,c]	0.000*
LDL (mmol/L)	3.22±0.92 [a,c]	2.60±0.63 [b]	2.52±0.57 [b]	0.002*
Tchol:HDL	3.96±1.63	3.76±0.99	4.22±0.71	0.391
LDL:HDL	2.20±1.29	2.11±0.79	2.62±0.65	0.128

* significant at $p\leq0.05$

a = significantly different from control, b = significantly different from Naive diabetic group, c = significantly different from diabetic subjects under treatment group

Key: n=sample size, BMI= Body mass Index, FBS= Fasting blood sugar, TChol= Total Cholesterol, TAG=Triglyceride, HDL= High Density Lipoprotein, LDL=Low Density Lipoprotein

Table 3 shows a significant positive correlation between copeptin and TAG in non-obesed diabetic subjects. No significant association was observed in the levels of FBS and copeptin when they were correlated with other parameters in both obesed and naïve diabetic subjects as it was illustrated in table 4 and 5 respectively. So also, there was a significant positive correlation between copeptin and TAG, while FBS shows a significant negative correlation with TAG in diabetic subjects under the treatment group as it was shown in table 6. The diagnostic performance of copeptin and FBS were determined. FBS had a superb higher area under the ROC curve (AUROC) of 0.503 than copeptin with area 0.297 (Figure 1).

Table-3: Correlation of plasma levels of FBS and Copeptin in Non- obesed diabetic subjects with other parameters

	FBS		Copeptin	
	r-value	p-value	r-value	p-value
BMI (Kg/m^2)	-0.247	0.246	0.063	0.771
FBS (mmol/L)	1.000	-	-0.340	0.104
Copeptin (pmol/L)	-0.340	0.104	1.000	-
TChol (mmol/L)	-0.165	0.441	0.252	0.234
TAG (mmol/L)	-0.463	0.023	0.511	0.011*
HDL (mmol/L)	0.035	0.872	0.045	0.836
LDL (mmol/L)	-0.086	0.688	0.184	0.389
* correlation is significant at the 0.05 level (2-tailed)				

Table-4: Correlation of plasma levels of FBS and Copeptin in Obesed diabetic subjects with other parameters

	FBS		Copeptin	
	r-value	p-value	r-value	p-value
BMI (Kg/m^2)	0.359	0.172	-0.230	0.391
FBS (mmol/L)	1.0	-	0.102	0.708
Copeptin (pmol/L)	0.102	0.708	1.000	-
TChol (mmol/L)	-0.493	0.052	-0.288	0.279
TAG (mmol/L)	0.041	0.880	0.350	0.184
HDL (mmol/L)	-0.241	0.368	-0.135	0.617
LDL (mmol/L)	-0.090	0.741	-0.256	0.338
* correlation is significant at the 0.05 level (2-tailed)				

Table-5: Correlation of plasma levels of FBS and Copeptin in Naive diabetic subjects with other parameters

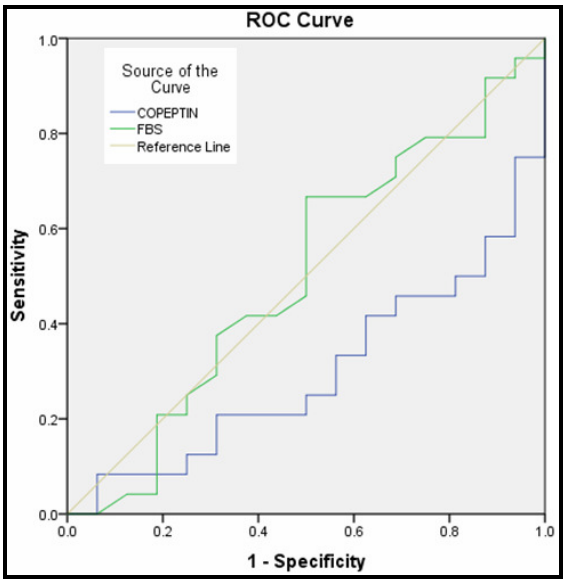
	FBS		Copeptin	
	r-value	p-value	r-value	p-value
BMI (Kg/m^2)	0.329	0.135	-0.055	0.806
FBS (mmol/L)	1.000	-	0.186	0.406
Copeptin (pmol/L)	0.186	0.406	1.000	-
TChol (mmol/L)	-0.197	0.380	-0.038	0.867
TAG (mmol/L)	0.074	0.743	0.354	0.106
HDL (mmol/L)	-0.007	0.976	0.024	0.915
LDL (mmol/L)	0.034	0.880	-0.006	0.980
* correlation is significant at the 0.05 level (2-tailed)				

Table-6: Correlation of plasma levels of FBS and Copeptin in Diabetic mellitus under treatment with other parameters

	FBS		Copeptin	
	r-value	p-value	r-value	p-value
BMI (Kg/m^2)	-0.267	0.283	0.062	0.807
FBS (mmol/L)	1.000	-	-0.357	0.145
Copeptin (pmol/L)	-0.357	0.145	1.000	-
TChol (mmol/L)	-0.221	0.378	0.233	0.351
TAG (mmol/L)	-0.500	0.035*	0.545	0.019*
HDL (mmol/L)	-0.110	0.665	0.014	0.955
LDL (mmol/L)	-0.160	0.526	0.221	0.378

* correlation is significant at the 0.05 level (2-tailed)

Fig-1: The ROC Curve of blood levels of Copeptin and FBS as diagnostic tool in Diabetic subjects



Discussion

Dyslipidemia was found to be highly prevalent in Nigeria with 90.7% [3] and 90.3% in South Africa [27]. Dyslipidemia has been noted to play an integral role within the pathogenesis and progression of micro and macrovascular complications in DM patients. There is enough evidence indicating a high-fat diet because of the major explanation for obesity and insulin resistance. Obesity is understood to be related to dyslipidemia, which may be a metabolic abnormality resulting in a persistent increase within the plasma concentration of cholesterol and triglyceride [5]. In this study, there was a bit higher in mean values of BMI (Body mass index), FBS (Fasting blood sugar), copeptin, TChol (Total cholesterol), HDL (High density lipoprotein) and LDL (Low density lipoprotein) in both Obesed and non-obesed diabetic subjects in comparison to the control group ($p<0.05$). Hypothalamic-pituitary-adrenal(HPA) activity has been known to reinforce in type 2 diabetic patients with diabetes complications and therefore the degree of cortisol secretion is said to the presence and number of diabetes complications [23] and Adediji et al. [10] attributed this to diabetes stress. Also, glucocorticoid secretion has been suggested to be a possible link between insulin resistance and metabolic syndrome clinical features like hypertension, obesity, coronary heart condition, hyperlipidemia and sort 2 diabetes [21, 28].

In our study, we evaluated copeptin levels during a sample of type 2 diabetic subjects with obesed, non-obesed and non-diabetic subjects as a control group. We found that both diabetic subjects with obesed and non-obesed have elevated copeptin levels when it had been compared with non-diabetic groups, whereas in diabetic subjects with obesed had higher copeptin levels than a non-obesed diabetic. Our observations actually confirm the role of Copeptin as a stress biomarker which has been reported to be gradually increased with increasing levels of stress and inflammation and will thus function as a surrogate biomarker for cortisol [16, 29]. This present study is in agreement with some authors finding an enhanced HPA axis activity [23, 30] and had conflicting results with other failing to point out any alteration [31]. Additionally, during this study, the serum

lipid abnormalities in type 2 diabetic patients with both obesed and non-obesed was a sign that dyslipidemia occurs as a result of metabolic derangement which is essentially thanks to insulin resistance resulting in a defect in lipid handling. Insulin resistance, relative insulin deficiency, and obesity are related to hypertriglyceridemia, low serum HDL cholesterol concentrations, and infrequently high serum rarity lipoprotein (LDL) cholesterol and lipoprotein values [3, 32].

Similarly, this study also showed statistical significance in copeptin and atherogenic indices among naïve diabetic subjects compared with those under treatment; so also with non-diabetic controls. The high risk of atherogenicity related to the tiny dense LDL particles has resulted in an emphasis on the aggressive lowering of LDL-C to therapeutic targets among patients with DM [24] more so since this pattern of lipid abnormalities are often detected before the onset of overt hyperglycemia. Thus early diagnosis and management of diabetes would go a really great distance in minimizing the rate of atherogenicity and associated clinical features. Furthermore, our study showed that copeptin had a direct correlation with triglycerides in obesed diabetic subjects. This further corroborated Andrews et al. [28] that reported that glucocorticoid secretion features a possible link between insulin resistance and metabolic syndrome. This assertion actually corroborated a view that a prime fat diet is a major explanation for obesity and insulin resistance as reported by Jisieike-Onuigbo et al. [3] and Suneetha [4]. Finally, the diagnostic performance of copeptin and FBS in the diabetic group decided. The area under the Receiver Operating Curve (AUROC) showed that FBS still remains a biomarker to hammer in the diagnosis of DM with the higher area under the ROC curve (AUROC) of 0.503 than copeptin with area 0.297. During this study, copeptin wasn't a sensitive and accurate marker of diagnosis as compared with fasting blood glucose in the diagnosis of DM when the diagnostic performance decided contrary to earlier studies in patients with severe bacterial sepsis [33] and severe leptospirosis [34].

Conclusion

This study shows that diabetic subjects have higher levels of copeptin and atherogenic indices when it's compared with non-diabetic groups. This actually confirmed that copeptin is related to dyslipidemia which is one among an indicator for top risk of atherogenicity, especially in obesed diabetic subjects that had higher copeptin levels than non-obesed diabetes. Also, copeptin was not found to be a more accurate marker of diagnosis for DM when its diagnostic performance with fasting blood glucose decided.

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