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Comparative Analysis Of Atherogenic Index Of Plasma And Its Relationship With Cardiovascular Risk Among Patients With Diabetes Mellitus And Concurrent Diabetes Mellitus With Hypertension Attending Endocrinology Clinic In A Tertiary Hospital South- South Nigeria

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Abstract: *Insulin resistance, found in type 2 diabetes mellitus is often associated with increased triglyceride (TG) and decreased HDL-cholesterol (HDL-C) and LDL-cholesterol (LDL-C). The atherogenic index of plasma (AIP), defined as logarithm [log] of (TG/HDL-C), has recently been proposed as a predictive marker for plasma atherogenicity and is positively correlated with cardiovascular disease risk. To determine the relationship between AIP and cardiovascular risk among patients with type 2 diabetes mellitus and concurrent diabetes mellitus with hypertension. This was a prospective study of type 2 diabetes mellitus patients attending the endocrinology clinic in University of Calabar Teaching Hospital (UCTH), Calabar over 4 month period from January to May 2015. Data was analysed using SPSS version 18. Female preponderance of 93 (71.5%) with males 37 (28.5%). The mean age was significantly higher in concurrent DM and HTN group than DM group alone (57.92 ± 9.21 versus 5338 ± 9.68, p < 0.05). Also, weight, BMI, and WHR were significantly higher in concurrent DM and HTN group, the level of dyslipidaemia was more in the same group, while AIP risk is higher in same group than in DM group alone (56.25% versus 43.75%). BMI and TG are positively correlated with AIP, while HDL is negatively correlated (p < 0.05). In conclusion, patients with concurrent DM and HTN have more dyslipidaemia and higher AIP risk which portend a higher cardiovascular disease risk.*

Keywords *– Atherogenic index of plasma, Cardiovascular risk, Diabetes mellitus, Hypertension.*

I. Introduction

Epidemiological studies have demonstrated that type 2 diabetes mellitus (DM) is a well-known risk factor for the development of cardiovascular disease, cerebrovascular disease, and peripheral vascular diseases. Alterations in lipid and lipoprotein profile contribute to atherosclerosis in type 2 diabetes [1].

Diabetes mellitus is a well known cause for cardiovascular diseases (CVD) and atherogenic dyslipidemia of diabetes also known as diabetic dyslipidemia is characterized by elevated very low density lipoprotein (VLDL), small dense low density lipoprotein (LDL) and low high density lipoprotein (HDL) levels, which constitute the lipid triad and are considered as traditional risk factors for CVD[2]. Lipid ratios have also been found to indicate an atherogenic risk and are said to better predictors of coronary artery diseases than lipids alone.

Although the major focus on the connection between lipids and coronary heart disease (CHD) is on LDL-cholesterol (LDL-C), the Adult Treatment Panel III has recognized the important roles of HDL-C and TGs, calling this combination an atherogenic dyslipidemia [3].

The atherogenic index of plasma (AIP), defined as logarithm [log] of the ratio of plasma concentration of triglycerides to high-density lipoprotein (HDL) cholesterol, has recently been proposed as a predictive marker for plasma atherogenicity and is positively correlated with cardiovascular disease risk [4].

Also, the ratio log (TG/HDL), which is called AIP correlates well with the size of HDL and LDL particles and with the fractional esterification rate of cholesterol by lecithin: Cholesterolacyl transferase in plasma.This ratio accurately reflects the presence of atherogenic small LDL and HDL particles, is a sensitive predictor of coronary atherosclerosis and cardiovascular risk [5] and a useful surrogate for insulin resistance [6].

More so, diabetes mellitus and hypertension has been shown to co-exist in a number of patients. About 10 to 15% and 1 to 2% of Nigerians have hypertension and diabetes mellitus respectively [7, 8]. Both conditions coexist frequently in this population, the prevalence of hypertension among diabetics being 20-40% [9, 10].

Several studies established a direct relationship between insulin resistance, enhanced sympathetic nervous activity, hypertension (HTN) and type 2 diabetes [11, 12].

Dyslipidaemia in type 2 diabetes and hypertension are both quantitative and qualitative [13-15]. Quantitative abnormalities include increased levels of total plasma cholesterol, triglyceride and low density lipoprotein

(LDL) cholesterol, and decreased level of high-density lipoprotein (HDL) cholesterol. Qualitative abnormalities include changes in the composition of LDL-cholesterol (small dense LDL-cholesterol, increased triglyceride content and increased electronegativity of LDL-cholesterol). These changes make LDL-cholesterol
susceptible to oxidation and glycation, with consequential foam cell formation, endothelial dysfunction and atherosclerosis[13,15,16].

The study on plasma lipid concentrations, prevalence of dyslipidaemia and AIP among patients with type 2 diabetes mellitus with or without hypertension is important. Several reports have shown that diabetes and hypertension are independently associated with dyslipidaemia among Nigerians [17-20]. Data on lipid patterns and atherogenic index of plasma among diabetic hypertensives in Nigeria is, however, scanty and limited to total plasma cholesterol [21, 22].

In view of the association between type 2 diabetes and hypertension and dyslipidaemia,[14.15,17-20] the role of lipid abnormalities as risk factors for atherosclerotic complications of diabetes and hypertension[13-16] and the additive nature of these complications when both conditions occur concurrently,
[23, 24], it may be proposed that putative increases in plasma lipid concentrations would occur in diabetic hypertensives [25].

The objective of this study is to determine and compare the quantitative lipid abnormalities and atherogenic index of plasma among type 2 diabetes mellitus with and without hypertension, with a view of determining cardiovascular risk in them.

II. Materials And Method

This is a prospective and comparative study carried out over a 4 month period from January to May 2015 of all diabetic patients aged 40 years and above attending the endocrinology clinic of University of Calabar Teaching Hospital.

Patients recruited were indigenous Nigerian normotensive type 2 diabetes mellitus patients and patients with concurrent type 2 diabetes mellitus and hypertension. A total of 130 patients were recruited for the study of which 65 had DM alone and the other 65 had concurrent DM and HTN.

The diagnosis of diabetes mellitus was based on the World Health Organisation criteria [26]. Patients on oral hypoglycaemic drugs or whose diagnoses of diabetes was made at the age of 40 years and above were considered to have type 2 diabetes mellitus. Systolic blood pressure > 140mmHg and/or diastolic blood pressure > 90mmHg measured using standard procedures were used to make a diagnosis of hypertension [27]. Height and weight were measured to the nearest centimetres and grams respectively with the subjects lightly clothed and without shoes. Body mass index (BMI) was then calculated as weight in kilograms divided by the square of height in metres.

The waist-hip ratio was also calculated by dividing waist circumference by hip circumference with normal values of ≤ 0.9 and ≤ 0.85 for males and females respectively [28].

2.1. Definition Of Dyslipidaemia

Dyslipidaemia is defined using the National Cholesterol Education Program – Adult Treatment Panel III (NCEP – ATP III) [29] as shown below:

- Total cholesterol (TC) $\geq$ 5.2mmol/l
- High density lipoprotein (HDL) cholesterol < 1.0mmol/l
- Low density lipoprotein (LDL) cholesterol $\geq$ 2.6mmol/l
- Triglyceride (TG) $\geq$ 1.7mmol/l

Also, the atherogenic index of plasma is defined as high risk when AIP $\geq$ 0.24 [30].

2.2. Laboratory Evaluation

The blood for serum lipid profile was collected in plain bottles. Serum total cholesterol (TC) and triglyceride (TG) were determined by enzymatic estimation while high density lipoprotein cholesterol (HDL-c) was determined by enzymatic estimation after precipitation [31, 32, 33]. Low density lipoprotein cholesterol (LDL-c) was determined from the values of the aforementioned using the Friedewald's formula [34] as follows:
VLDL = TG ÷ 5, LDL = Total Cholesterol (TC) – (VLDL +HDL).
Atherogenic index was calculated by using base 10 logarithm of the ratio of TG to HDL [5], formula = log (TG/HDL-C).

2.3. Statistical Analysis

Data entry and analysis were done using Statistical Package For Social Sciences (SPSS) version 18. Means are presented as values ± standard deviation. Student's t-test and chi -square test were used to compare means and proportions between two groups respectively. Analysis of variance (ANOVA) and correlations were used as appropriate.

III. Results

A total 130 patients were recruited for the study comprising of 37 males and 93 females with a mean age of 55.65 ± 9.68 years but the mean age of the patients with diabetes mellitus and hypertension is significantly higher than those with diabetes mellitus alone (57.92 ± 9.21 versus 53.39 ± 9.68, $p < 0.05$). Diabetes mellitus patients with hypertension had a longer duration of DM compared with those with DM alone but were not statistically significant (8.49 ± 6.70 versus 7.17 ± 4.95, $p > 0.05$). More so, the weight, BMI, WHR, systolic and diastolic blood pressures were significantly higher in those with concurrent diabetes mellitus and hypertension, than in those with diabetes mellitus alone ($p < 0.05$). Patients with concurrent diabetes mellitus and hypertension had a high atherogenic index risk 18(56.3%) as compared to those with diabetes alone 14(43.8%) while chronic complications were more in patients with diabetes mellitus alone 52(52.0%) than in those with diabetes mellitus and hypertension 48(48.0%).

Table1: Demographic and Clinical Characteristics of Patients

Parameters	DM N=65 Mean ±SD, %	DM + HTN N= 65	p - value
Sex			
Male	21(56.8%)	16(43.2%)	0.331
Female	44(47.3%)	49(52.7%)	
Duration of Diabetes Mellitus	7.17 ± 4.95	8.49 ± 6.70	0.203
Chronic Complication			
Present	52(52.0%)	48(48.0%)	0.405
Absent	13(43.3%)	17(56.7%)	
Age (years)	53.38 ± 9.68	57.92 ± 9.21	0.007
Weight (kg)	67.48 ± 10.77	76.09 ± 15.10	< 0.001
Body mass index(kg/m^2)	25.81 ± 3.42	29.71 ± 5.93	< 0.001
Waist hip ratio(WHR)	0.89 ± 0.049	0.93 ± 0.047	< 0.001
Systolic BP(mmHg)	116.15 ± 14.97	139.23 ± 25.02	< 0.001
Diastolic BP(mmHg)	75.54 ± 10.61	83.23 ± 17.24	0.003
Atherogenic index risk			
Low risk(-0.3 – 0.1)	30(47.6%)	33(52.4%)	
Medium risk(0.11 – 0.24)	21(60.0%)	14(40.0%)	0.360
High risk(Above 0.24)	14(43.8%)	18(56.3%)	

Comparison of the biochemical parameters showed that the levels are higher in patients with concurrent diabetes mellitus and hypertension, than those with diabetes mellitus alone but not statistically significant ($p > 0.05$)

Table 2: Comparison of Biochemical Parameters of Patients

Parameters	DM N=65	DM + HTN N=65	p -value
FBS(mmol/l)	10.2 ± 4.79	10.47 ± 5.13	0.756
HbA1c (%)	8.04 ± 3.01	8.21 ± 3.23	0.757
TC(mmol/l)	4.71 ± 0.89	4.99 ± 0.88	0.071
HDL(mmol/l)	1.29 ± 0.31	1.34 ± 0.34	0.379
LDL(mmol/l)	2.80 ± 0.68	2.87 ± 0.73	0.571
TG(mmol/l)	1.56 ± 0.62	1.77 ± 0.74	0.084
AIP	0.054 ± 0.26	0.098 ± 0.25	0.316

In the bivariate correlation analysis, with AIP as the dependent variable, the weight, BMI and TG are strongly positively correlated ($p < 0.05$) while the HDL is negatively correlated ($p < 0.05$).

Table 3: Correlation of Artherogenic Index of Plasma With Clinical and Biochemical Parameters

Value	Correlation value (R)	p -value
Age	0.133	0.131
Weight	0.297**	0.001
BMI	0.298**	0.001
WHR	0.035	0.692
Duration of DM	-0.049	0.577
FBS	-0.141	0.109
HbA1c	-0.141	0.110
TC	0.143	0.105
HDL	-0.661**	< 0.001
LDL	0.025	0.779
TG	0.858**	< 0.001
Systolic BP	0.157	0.074

Diastolic BP	0.151	0.086

The prevalence of dyslipidaemia is shown in table 4 in which patients with DM and HTN have higher values of total cholesterol, LDL-cholesterol and TG as compared to those with DM alone (Borderline TC 62.8% versus 37.2%, High TC 60.0% versus 40.0%, Borderline LDL 51.7% versus 48.3%, High TG 61.1% versus 38.9%).

More so, the prevalence of HDL is lower in patients with DM alone (55.6%) while AIP risk is higher in patients with DM and HTN (56.25%).

Table 4: Prevalence of Dyslipidaemia Among DM and DM + HTN Patients

Parameters	DM (%)	DM + HTN (%)	Total
TC (mmol/l)			
< 5.2 (Desirable)	47 (57.3)	35 (42.7)	82
5.2 – 6.2 (Borderline)	16 (37.2)	27 (62.8)	43
> 6.2 (High)	2 (40.0)	3 (60.0)	5
HDL (mmol/l)			
< 1.0 (Low)	10 (55.6)	8 (44.4)	18
>1.0 (High)	55 (49.1)	57 (50.9)	112
LDL (mmol/l)			
< 2.6 (Desirable)	22 (53.7)	19 (46.3)	41
2.6 – 4.1 (Borderline)	42 (48.3)	45 (51.7)	87
> 4.1 (High)	1 (50.0)	1 (50.0)	2
TG (mmol/l)			
< 1.7 (Desirable)	33 (53.2)	29 (46.8)	62
1.7 – 2.2 (Borderline)	25 (50.0)	25 (50.0)	50
> 2.2 (High)	7 (38.9)	11 (61.1)	18
AIP risk			
-0.3 – 0.1 (Low)	30 (47.6)	33 (52.4)	63
0.11 – 0.24 (Medium)	21 (60.0)	14 (40.0)	35
> 0.24 (High)	14 (43.75)	18 (56.25)	32

($P > 0.05$)

IV. Discussion

In our study, we found significant increase in the age, weight, BMI, WHR and blood pressure values in patients with concurrent DM and HTN as compared to those with DM alone. The increase in these values among patients with DM and HTN may be due to the longer duration of DM with poor glycaemic and blood pressure control which may be associated with metabolic and cardiovascular conditions such as obesity and hypertension respectively. A similar observation of poor glycaemic and blood pressure control was noted in a Nigerian study in spite of commencement on medications [25].

The female preponderance in our study is similar to a clinic based study in patients with DM, and concurrent HTN and DM in our environment [25]

This study further demonstrated that the levels of TC, HDL, LDL, TG, atherogenic index of plasma, atherogenic index risk and prevalence of dyslipidaemia do not differ signicantly among the patients with concurrent diabetes mellitus and hypertension, and those with diabetes mellitus alone.

Two reports on the comparative profile of patients with diabetes mellitus and those with concurrent diabetes mellitus and hypertension showed that the plasma lipid concentrations, AIP, prevalence of dyslipidaemia do not differ significantly between the groups[25] , while the other report showed that total plasma cholesterol did not differ significantly between the groups (4.6 ± 1.2 versus 4.6 ± 0.8mmol/l) [21].

The absence of significant increases in plasma lipid profile levels in patients with concurrent type 2 diabetes and hypertension demonstrated in this study supports previous report [35] that neither hyperglycaemia nor elevated blood pressure is responsible for hyperlipidaemia among patients with diabetes or hypertension.

According to our study, AIP is significantly and positively correlated with weight, BMI and TG but inversely correlated with HDL. A report observed that an increasing atherogenic index is associated with an increase in BMI and this index is a significant indepent predictor of CHD [36, 37].

Dobiasova and Frohlich proposed the term Atherogenic Index of Plasma (AIP), to consider the risk of triglyceride and defined as log (TG/HDL-C), with the view that people with high AIP have a higher risk for coronary artery disease than those with low AIP, that AIP is positively correlated with the fractional esterification rate of HDL (FERHDL), and is inversely correlated with LDL particle size. Moreso, FERHDL predicts particle size in HDL and LDL, which in turn predicts the risk of coronary heart disease, therefore the use of TGs and HDL-C as AIP may be useful in predicting plasma atherogenicity. Also, insulin resistance (decreased insulin sensitivity), which has been shown to be accompanied by increased coronary artery disease risk, is also often associated with increased TG and decreased HDL-C concentrations with a predominance of small , dense LDL particles. In view of this, calculating AIP can be more reliable in predicting the risk for development of atherosclerosis in diabetes mellitus patients [5].

The existence of a link between diabetes, hypertension, and dyslipidaemia has been clearly described among Caucasians [11, 12]. The recognized role of genetically determined insulin resistance that has been shown as a common pathogenic mechanism underlying the process of dyslipidaemia, diabetes, and hypertension in human metabolic syndrome [11] may be an explanation to the lack of additional increases in plasma lipid concentrations when type 2 diabetes mellitus and hypertension occur concurrently.

In Nigeria, few studies were carried out on AIP in relation to cardiovascular risk in type diabetes mellitus, most studies were done on individual lipid parameters in diabetic patients with or without hypertension [19 – 22]. However, some studies on AIP were done in other group of patients and other lipid profile ratios were compared to AIP in determining cardiovascular risk in these patients [38, 39]. The resultant effect is the paucity of literatures on AIP that is calculated as log (TG/HDL-C) in type 2 diabetes mellitus patients.

The present study is therefore, a contribution to the determination and identification of values of lipid profile, particularly log (TG/HDL-C) that may be associated with cardiovascular events among type 2 diabetes mellitus patients in our environment.

V. Conclusion

Dyslipidaemia is common in diabetes mellitus patients with or without hypertension. However, concurrent diabetes mellitus and hypertension does not result in excess hyperlipidaemia than when either of the two conditions occurs in isolation. AIP which can easily be calculated from standard lipid profile can act as an adjunct that significantly adds predictive value for cardiovascular events beyond that of the individual lipid parameters.

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