

Correlations of Remnant Cholesterol and Atherogenic Index of Plasma as Predictors of Cardiovascular Accidents in Obese and Overweight Individuals in Nigeria

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ABSTRACT

Obesity is one of the indices of metabolic syndrome and has been implicated in cardiovascular incidents. Atherogenic index of plasma (AIP) has been associated as a biomarker in the predictor of cardiovascular diseases, with remnant cholesterol (RC) suggested as a link to the development of cardiovascular incidents irrespective of body mass index.

Objective: The main aim of this current study was to investigate the correlation between AIP and RC among the participants.

Materials: A total of 90 participants with average age of $36.05 \pm$ for normal weight, 36.54 ± 0.7 for overweight and 37.85 ± 2.1 for obese, were enrolled into the study, the participants were categorized based on their BMI. AIP was calculated as $\text{Log}_{10}(\text{TG}/\text{HDLc})$, RC was calculated as $(\text{TC}-\text{HDLc}-\text{LDLc})$, fasting blood was collected for analysis of lipid profile, and fasting blood sugar by standard methods. Data obtained were analyzed using statistical packages for social sciences (SPSS) version 22.0.

Results: The values of basic lipid profile and their mathematical derivatives except HDLc were significantly higher in obese and overweight subject when compared to the control (normal weight). In the regression analysis, we found out that subjects with higher AIP shows a tendency of increased risk for the development of obesity and its related complications ($\text{OR}=2.74, <P 0.001$). AIP showed to be a better predictive value for obesity with AUC of 0.8, than other lipid components and derivatives. The Pearson correlation analysis indicates that AIP positively and significantly correlated with RC, BMI, Castelli index I and II, non-HDLc and VLDL and negatively correlated with HDLc across the group.

In this study, the analyzed Cardiovascular risk indices were indicative of atherogenicity risk which might help in identifying individuals with abnormal lipid composition at risk of cardiovascular diseases. Our findings suggested that lipid profile derivatives such as Remnant Cholesterol (RC), Atherogenic Index of Plasma (AIP) and Castelli index, could serve as more sensitive cardiovascular risk predictors in the presence of normal value of basic lipid panel test.

Keywords: Obesity, Atherogenic Index of Plasma, Remnant Cholesterol, Cardiovascular Disease, Metabolic Syndrome

Introduction

Obesity is a medical condition in which adipocytes exhibit hypertrophy and visceral adipose tissue accumulates due to high caloric intakes which exceeds expenditure [1]. Free fatty acids secreted from adipose tissue form the major products of lipid metabolism and any alteration results in its abnormal heightened metabolism and circulation contributes to the development of metabolic disorders [2]. Studies have reported the correlation

of lipids with metabolic syndrome [2-4]. This assertion implies that lipid components in blood such as TC, LDLc, HDLc, TG and their calculated derivatives are biomarkers to predict cardiovascular incidents and other metabolic syndrome.

In individuals with type 2 diabetes, metabolic syndrome with combined dyslipidemia and cardiovascular risk is increased by a cluster of risk factors such as abdominal obesity, impaired fasting glucose, increased blood pressure, low HDLc, increased Triglyceride and an increased in small dense LDL particles [5]. Tan et al, in their studies showed the practical use of AIP for

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assessing these changes in lipoprotein profile, using results of standard assays [5,6].

Remnant Cholesterol (RC) is a very atherogenic lipoprotein composed primarily of very low-density lipoprotein (VLDL), intermediate density lipoprotein (IDL) and chylomicrons, it can therefore be described as plasma cholesterol devoid of low-density lipoprotein (LDL) or High-density lipoprotein (HDL) [7,8]. According to a study, high Remnant Cholesterol is more predictive of myocardial infarction than any other lipid particle, it has been suggested to be predictive of coronary artery disease in patients with normal total cholesterol [9-11].

Atherogenic Index of Plasma (AIP) calculated as $\log_{10}(\text{TG}/\text{HDLc})$ which reflects the level of TG and HDLc, has been indicated as a biomarker for the prediction of dyslipidemia, cardiovascular disease and metabolic disease risks, Zhu X et al in their studies also indicated that AIP is strongly related to obesity [3,4,12,13].

Therefore, this study aims to assess the association between AIP and Remnant Cholesterol among the overweight and obese subjects in Nnewi eastern Nigeria.

Materials and Methods

Study Design

This was a comparative cross-sectional study. A total of 90 consenting participants were recruited who fulfilled the inclusion criteria. The study protocol was approved by Nnamdi Azikiwe University Teaching Hospital with reference number NAUTH/CS/66/vol.11/154/2018/088.

Data Collection

Participants base line data which include Age, Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), Height, Weight and Waist and Hip circumference were obtained while laboratory analysis of baseline lipid profile, (TC, TG, HDLc) and fasting blood glucose (FBG) were carried out using standard spectrophotometric methods. VLDL was calculated using Friedwald formula. Hypertension was defined as systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg. Diabetes mellitus (DM) was defined as self-indicated, fasting blood glucose ≥ 126 mg/dl or the use of oral anti-diabetic drugs. Dyslipidemia was defined as self-indicated, LDLc ≥ 130 mg/dl, HDLc ≤ 40 mg/dl, in men or ≤ 50 mg/dl in women, TG ≥ 150 mg/dl, and TC ≥ 200 mg/dl, or the use of anti-lipidemic medications. All the participants fasted for 8-12hours before blood was drawn for laboratory analysis. 7ml of venous blood was drawn from the median cubital vein from subjects after an overnight fast of 8-12 hours. 2ml was transferred to a tube containing glucose additive (fluoride oxalate) and 5ml was transferred to a plain tube. The sample were centrifuged at 2000 rotation per minute for 15 minutes, after which the serum samples were extracted and stored at -20°C until analysis and values recorded.

Definition of Calculated Parameter

AIP; Atherogenic index of plasma was calculated as $\log_{10}(\text{TC}/\text{HDLc})$

RC; Remnant Cholesterol was calculated as $(\text{TC}-\text{HDLc}-\text{LDLc})$
Castelli risk index CRI was calculated as
CRI I was calculated as (TC/HDLc)
CRI II was calculated as $(\text{LDLc}/\text{HDLc})$.

Statistical Analysis

SPSS version 22.0 was used for statistical analysis, one-way ANOVA was used to compare the variables. Correlation of AIP with the cardiovascular parameters was expressed using Pearson correlation coefficient. All statistical test were two sided and a p-value of <0.05 was considered significant.

Results

A total of 90 subjects participated in the study, each consisting of 30 normal weight subjects with a mean age of 36.05 ± 0.5 , 30 overweight subjects with mean age of 36.54 ± 0.7 and 30 obese subjects with mean age of 37.85 ± 2.1 . They were categorized using their mean BMI, 21.75 ± 1.82 for normal weight, 27.11 ± 1.02 for overweight and 33.85 ± 4.51 for obese subjects respectively. Table 1 shows the anthropometric data of the participants, there was a significant difference in the systolic blood pressure (SBP) diastolic blood pressure (DBP) Body mass index (BMI) waist to hip ratio (WHR) of the obese and overweight participants when compared to the control (normal weight) subjects ($P < 0.05$). Table 2 shows the data on cardiovascular risk factors among the participants, we observed significant increase in VLDLc, TG, AIP and FBG of the obese and overweight when compared to the control (normal weight) subjects ($P < 0.05$). Other cardiovascular risk indicators such as HDLc, LDLc, Non-HDLc, TC/HDLc LDL/HDLc and Remnant Cholesterol were found to be statistically insignificant when compared among the groups.

Table 3 shows the correlation of AIP with other cardiovascular risk factors. We observed that AIP significantly correlated negatively with HDLc, negatively with TG and TC in the control group and positively in the overweight and obese group which was found to be insignificant. There was a positive significant correlation of AIP with RC across the group. Positive correlation was observed with BMI, VLDLc, Non-HDLc and Castelli index I and II across the group. AIP correlated significantly positively with LDLc only in the control group but do not correlate with LDLc values in overweight and obese groups.

Table 4 shows the results of logistic regression analysis. Univariate regression analysis showed that HDLc, LDLc, VLDLc, Castelli index I and II, Remnant Cholesterol and Atherogenic Index of Plasma were strongly associated with Obesity. The odd of obesity was high when associated with high level of AIP. OR = (2.74, $P < 0.001$).

Table 5 and figure 1 shows the AUC values of ROC were calculated to compare the predictive value between AIP and the following lipid components and mathematical derivatives, (RC, LDLc, VLDLc, HDLc, TC, TG and Castelli index I and II) for predicting obesity. From the AUC all the lipid parameters showed statistical significance, but AIP showed a high predictive index, with an AUC of 0.80.

Table 1: Anthropometric Data of The Overweight and Obese Participants Compared to The Control (Normal Weight) Participants

parameters	Normal weight (A)	Overweight (B)	Obese(C)	F-value	P-value	AvsB	AvsC	BvsC
SBP mmHg	115.28±11.89	118.92±25.0	127.00±10.8	3.310	0.042*	1.000	0.040*	0.287
DBP mmHg	75.59±10.03	78.40±9.55	85.64±12.25	6.246	0.003*	1.000	0.003*	0.050*
BMI kg/m ²	21.75±1.82	27.11±1.02	33.85±4.51	123.38	0.001*	0.001*	0.001*	0.001*
WHR	0.85±0.05	0.86±0.07	0.96±0.10	18.038	0.001*	1.000	0.001*	0.001*
AGE yrs	36.05±1.5	36.54±0.7	37.85±2.1	120.04	0.083	0.23	0.083	1.000

SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, BMI: Body Mass Index, WHR: Waist-Hip Ratio

Table 2: Data of Cardiovascular Disease Risk Factors

parameters	Normal weight (A)	Overweight (B)	Obese(C)	F-value	P-value	AvsB	AvsC	BvsC
HDLc mmol/l	1.10±0.21	0.95±0.009	1.00±0.17	0.816	0.446	0.732	1.000	0.906
LDLc mmol/l	1.77±0.67	1.52±0.34	1.84±0.38	3.006	0.055	0.201	1.000	0.067
VLDL mmol/l	0.47±0.22	0.76±0.31	0.82±0.23	9.391	0.001*	0.001*	0.001*	0.019*
TG mmol/l	1.09±0.51	1.72±0.06	1.85±0.59	8.638	0.001*	0.001*	0.001*	0.030*
TC mmol/l	3.39±0.66	3.47±0.42	3.45±0.53	0.135	0.874	1.000	1.000	1.000
Non-HDL	2.39±0.45	2.52±0.33	2.45±0.36	0.501	0.608	0.960	1.000	1.000
TC/HDL	3.08±0.67	3.65±0.42	3.45±0.32	1.357	0.264	0.413	1.000	0.534
LDL/HDL	1.61±0.70	1.60±0.42	1.84±0.26	1.558	0.217	0.457	0.072	0.331
RC mmol/l	0.50±0.28	0.69±0.46	0.72±0.40	2.853	0.064	0.199	0.095	1.000
AIP mmol/l	0.037±0.01	0.26±0.05	0.26±0.06	7.704	0.001*	0.027*	0.017*	0.010*
FBG mmol/l	3.46±0.79	4.46±1.82	4.94±1.26	8.740	0.001*	0.021*	0.001*	0.647

AIP: Atherogenic Index of Plasma, BMI: Body Mass Index, RC; Remnant Cholesterol, LDLc Low Density Lipoprotein Cholesterol, HDLc: High Density Lipoprotein Cholesterol, TG; Triglyceride, TC: Total Cholesterol, VLDL: Very Low-Density Lipoprotein, FBG: Fasting Blood Glucose

Table 3: Correlation of Aip with Cvd Risk Factors

parameters	Normal weight		Over weight		Obese	
	r	p	r	p	r	p
AIP vs HDLc	-0.027	0.001*	-0.86	0.050*	-1.00	0.000*
AIP vs LDLc	0.45	0.000*	0.79	0.110	0.61	0.270*
AIP vs VLDLc	0.60	0.000*	0.35	0.050*	0.25	0.050*
AIP vs TG	-0.25	0.685	0.37	0.530	1.00	0.000*
AIP vs TC	-0.25	0.685	0.00	1.000	0.41	0.450
AIP vs non-HDLc	0.610	0.002*	0.25	0.000*	0.42	0.000*
AIP vs TC/HDLc	0.17	0.000*	1.00	0.001*	0.48	0.000*
AIP vs LDLc/HDLc	0.408	0.000*	0.25	0.001*	0.61	0.000*
AIP vs RC	0.37	0.001*	1.00	0.001*	0.22	0.001*
AIP vs BMI	0.79	0.000*	0.41	0.000*	0.25	0.000*

AIP: Atherogenic Index of Plasma, BMI: Body Mass Index, RC; Remnant Cholesterol, LDLc Low Density Lipoprotein Cholesterol, HDLc: High Density Lipoprotein Cholesterol, TG; Triglyceride, TC: Total Cholesterol, VLDL: Very Low-Density Lipoprotein.

Table 4: Logistic Regression Analysis of Aip and Other Cardiovascular Parameters

Parameter	Odd Ratio	95%CI	P-Value
HDLc (mmol/l)	0.85	0.84-0.86	<0.001*
VLDLc (mmol/l)	1.00	1.00-1.00	<0.001*
TG (mmol/l)	1.00	1.00-1.00	<0.001*
TC (mmol/l)	0.92	0.91-0.93	<0.001*
Non-HDLc	0.88	0.84-0.86	<0.001*
TC/HDLc	0.95	0.94-0.96	<0.001*
LDL/HDL	0.95	0.94-0.96	<0.001*
RC	1.00	1.00-1.00	<0.001*
BMI	0.94	0.93-0.95	<0.001*
AIP	2.74	1.80-3.68	<0.001*
LDLc (mmol/l)	1.00	1.00-1.00	<0.001*

AIP: Atherogenic Index of Plasma, BMI: Body Mass Index, RC; Remnant Cholesterol, LDLc Low Density Lipoprotein Cholesterol, HDLc: High Density Lipoprotein Cholesterol, TG; Triglyceride, TC: Total Cholesterol, VLDL: Very Low-Density Lipoprotein.

Table 5: Area Under the Roc Curve (95% Ci) For Obesity in Respect of Aip, Tc, Tg, Ldlc, Vldlc, Hdlc, Castelli Index I And II, And Rc

parameters	AUC (95%)	P-value	Sensitivity	Specificity
HDL (mmol/l)	0.71 (0.68-0.74)	<0.001*	0.75	0.70
VLDL (mmol/l)	0.48 (0.44-0.52)	<0.001*	0.42	0.42
LDL (mmol/l)	0.57 (0.52-0.62)	<0.001*	0.52	0.66
TC (mmol/l)	0.40 (0.35-0.45)	<0.001*	0.40	0.45
TG (mmol/l)	0.61 (0.58-0.64)	<0.001*	0.58	0.60
RC	0.74 (0.68-0.80)	<0.001*	0.65	0.50
AIP	0.80 (0.75-0.85)	<0.001*	0.75	0.70
TC/HDL	0.62 (0.58-0.66)	<0.001*	0.60	0.66
LDL/HDL	0.60 (0.55-0.65)	<0.001*	0.52	0.50

AUC; Area Under the Curve, AIP: Atherogenic Index of Plasma, RC; Remnant Cholesterol, LDLc Low Density Lipoprotein Cholesterol, HDLc: High Density Lipoprotein Cholesterol, TG; Triglyceride, TC: Total Cholesterol, VLDL: Very Low-Density Lipoprotein.

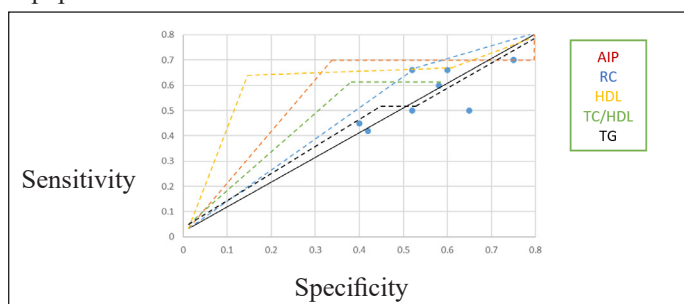


Figure 1: Shows the predictive activities of AIP and other lipid components in obesity

Discussion

We examined the relationship between AIP and RC in normal weight, overweight and obese individuals. Our results showed AIP to be a sensitive predictor of CVD in the presence of apparently normal HDLc value and correlated positively and significantly with Remnant cholesterol.

Studies have indicated that Dyslipidemia is a known risk factor for CVD a series of lipid panel test have been employed to predict the risk of cardiovascular diseases and these comprised majorly of plasma concentration of lipids and lipoprotein [9,14-16]. Currently the use of lipid mathematical derivatives as risk indices has been promising in the prediction of Cardiovascular risks/accidents in which many studies has shown relevance of the lipid ratios [15-17].

AIP described as log₁₀ (TG/HDLc) which was first described by Dobiasova and frolich, was found to be predictive of CVD risk when HDLc was observed to be normal across the group

we analyzed, this indicates that AIP is a sensitive marker of atherogenicity [4]. Dobiasova conjectured that AIP demonstrates as equilibrium between the definite concentration of serum HDLc and TG which might predetermine the direction of cholesterol transport in intra-vascular pool [4]. Some studies have demonstrated that AIP is associated with metabolic syndrome and increased body mass index [14,18]. This was reflected in our study where AIP correlated positively and significantly with BMI across the various group.

Our study found out that AIP was increased to high risk level in the overweight and obese group when compared with normal weight. This finding was in consonance with the study of Myat Su Bo et al, in which they found a positive correlation between AIP, BMI, and visceral fat [19].

From our regression analysis, we found out that subjects with higher AIP shows a tendency of increased risk for the development of obesity and its related complications, univariate logistic regression analysis results showed that AIP was an independent risk factor for obesity (OR=2.74, <P0.001), also AIP showed to be a better predictive value for obesity with AUC of 0.8, than other lipid components and derivatives, hence represents a better biomarker for obesity.

Furthermore, AIP has been suggested as a biomarker to predict obesity induced cardiovascular diseases than traditional lipid biomarkers, in which some studies has pointed out a sharp difference in the level of some lipid parameters such LDL, that is abnormally increased in coronary artery diseases (CAD) but in majority of CVD patients do not exhibit such elevated levels of LDL. This analogy was demonstrated in Framingham study cohort study which showed that 20% of myocardial infarction events occurred in patients whose average total cholesterol and LDLc level were lower than the recommended levels according to the guidelines of the national cholesterol education program [20,21]. This discovery showed that, it is not sufficient to use basic lipid profile parameters to predict obesity induced cardiovascular events.

In our study, we also observed a positive correlation of AIP with Remnant Cholesterol across the group, this is a significant finding because RC is an emerging marker in the assessment of cardiovascular incidents irrespective of BMI, this buttress the fact that AIP is a sensitive marker/predictor in subjects who might develop cardiovascular diseases [7,11].

In our study we also observed the significant elevation of AIP in groups where the baseline lipid profile parameters (TG, TC, LDLc, HDLc) seems to be normal. This implies that AIP can possibly serve as the Diagnostic alternative. AIP also correlated with Castelli Index I and II. This corroborates with the work of Da luz et al, in which they established that the ratio of TG/HDLc correlate with AIP [22]. A study by Nair et al also lends the evidence to this observation having noted an association between AIP and CR I and II which ultimately leads to the formation of atheromatous plaques [23].

As we have indicated previously, AIP correlated negatively and significantly with HDLc, positively and significantly with RC, Non-HDLc, BMI, Castelli index I and II. Also, AIP has the most

significant AUC (0.8) than other lipid biomarkers analyzed. The results show that, AIP is a better index of cardiovascular disease and a sensitive predictor of cardiovascular atherosclerotic risk, likewise Remnant Cholesterol is an emerging marker of cardiovascular accidents and Castelli index ratios are predictive of AIP, hence have the capacity to diagnosed subjects at the risk of obesity induced cardiovascular incidents [7,24].

Conclusion

In conclusion, our study revealed that calculated lipid ratios, (Remnant cholesterol, Atherogenic Index of Plasma, Castelli Index, and Non-HDLc) can be valuable in the assessment and diagnosis of subject at the risk of cardiovascular accident in this environment. We suggest, the calculation of lipid ratios and their addition to lipid panel test. This could help reduce mortality due to sudden cardiovascular incidents.

Limitations

The study encountered some limitations, which ranged from sample size, to confounding factors such as diet, physical activity, genetic factors and other demographic variables. Further studies can be conducted with larger population and the listed factors put into consideration.

Ethical Approval

Ethical approval was sought and obtained from the Ethics Committee (NAUTH/CS/66/VOL.11/154/2018/088) of Nnamdi Azikiwe University Teaching Hospital Nnewi.

Conflicts of Interest

The authors declare that there is no conflicts of interest.

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