UNDER PEER REVIEW

Original Research Article

ATHEROGENIC TRIAD IN OVERWEIGHT AND OBESE ADULTS IN SOUTH-SOUTH NIGERIA

Abstract

Context: Atherogenic triad is a constellation of lipid abnormalities characterized by elevated small, dense low density lipoprotein particles, decreased high density lipoprotein particles and hypertriglyceridaemia.

Aim: This study determined the prevalence of atherogenic triad among the overweight and obese adults in Benin-City, South-South, Nigeria.

Setting and design: Study was conducted among overweight and obese adults in Benin City. It is a cross-sectional study.

Materials and methods: This study was conducted among 138 overweight and obese adults in Benin- City, Nigeria between July and September, 2016. Concentration of small, dense LDL-cholesterol was determined using precipitation method involving sodium-heparin and manganese II chloride as described by Hirano *et al*. Subjects were categorized into three groups (ideal weight, overweight and obese) based on their body mass index.

Results: The mean small dense LDL-cholesterol levels in the three groups were 0.79 ± 0.16, 0.96 ± 0.15 and 1.33 ± 0.26 mmol/l respectively which were statistically different, triglyceride levels were 1.41±0.73, 1.33±0.61 and 1.31±0.73 mmol/L in the ideal weight, overweight and obese categories respectively while plasma HDL-cholesterol were 0.85± 0.20, 1.05±0.34 and 0.94±0.30 mmol/L in the ideal weight, overweight and obese groups respectively. Elevated LDL-cholesterol was seen in more than 80% of the normal weight and the obese subjects and; 57.8% of the overweight subjects. Two (3.6%) obese subjects had

UNDER PEER REVIEW

elevated sdLDL-C with LDL-C within the reference interval. Reduced HDL-C was found more in the normal weight and obese subjects while atherogenic triad was detected in 7 (15.2%) of the obese.

Conclusion: The prevalence of atherogenic triad among the obese adult was 15.2%. The prevalence of the atherogenic triad components were higher among the obese individuals than the overweight. There is an urgent need for introduction of therapeutic lifestyle modification among overweight and obese individuals in our population.

Key words: Atherogenic triad, overweight, obesity, small dense LDL-cholesterol, lipids.

Key message: Prevalence of atherogenic triad is high among the obese Nigerians. They are at risk of cardiovascular diseases.

Introduction

Atherogenic triad, otherwise known as dyslipidaemic triad or lipid triad comprises of elevated blood concentration of small, dense low density lipoprotein (sdLDL) particles, decreased high density lipoprotein particles and increased triglyceride.[1] These lipid abnormalities are typical features of obesity, metabolic syndrome, insulin resistance and type-2 diabetes mellitus.[2] The involvement of lipid triad in the aetiopathogenesis of cardiovascular diseases (CVD) has been well documented.[3] CVD are the major cause of morbidity and mortality worldwide with approximately 17.5 million deaths in 2005, among them, 7.6 million deaths from coronary heart disease and 5.7 million deaths from stoke. This figure has been projected to rise to 20 million deaths in 2015. [4]

Low density lipoproteins are primary plasma lipid carriers in humans comprising of two distinct subfractions: large buoyant LDL and small dense LDL particles[5] that vary in their size, density, physicochemical composition, metabolic behavior and atherogenicity. SdLDL are lipoprotein fraction with density ranging from 1.019 to 1.063 g/ml. sdLDL particle has

UNDER PEER REVIEW

recently emerged as an important risk factor for myocardial infarction and cardiovascular diseases.[2,6] Generally, LDL particles are classified into four subclasses. These include: large (LDL I), intermediate (LDL II), small (LDL III) and very small (LDL IV) LDL subfractions. The LDLIII and LDLIV constitute the small dense LDL particle commonly referred to as phenotype pattern B with peak diameter of ≤25.5 nm. Increased atherogenicity of sdLDL is based on their specific biochemical and biophysical properties. Its small size favors their penetration into the arterial wall where they serve as a source of cholesterol and lipid storage.[7] The association between lipids and coronary heart disease (CHD) has been well documented.[5]

Koba *et al*., reported that small dense LDL are more atherogenic than large buoyant (lbLDL), they readily penetrate the arterial wall, higher affinity for the intimal proteoglycans, prolonged plasma half-life than buoyant LDL, low affinity for LDL receptor, low resistance to oxidative stress than buoyant LDL and they are easily engulfed by macrophages.[8] SdLDL-C is elevated in patients with family history of premature coronary heart disease (CHD), hyperapobetalipoproteinaemia, familial combined hyperlipidaemia, familial dyslipidaemic hypertension, subclinical hypothyroidism and metabolic syndrome.[9] From genome-wide association studies, proprotein convertase subtilisin kexin type-7 (PCSK7) gene has been found to be associated with sdLDL-C and other lipid factors.[10]

Highly atherogenic sdLDL-C are generated from VLDLI particles by the action of lipoprotein lipase, cholesterylester transport protein (CETP) and hormone sensitive lipase.[11] Environmental factors, abdominal adiposity, oral contraceptive use, diabetes mellitus and high carbohydrate diets are associated with elevated sdLDL-C.[11] Gazi *et al.,* reported the acceptance by National Cholesterol Education Program (NCEP)-Adult Treatment Panel III (ATP-III) of the sdLDL-cholesterol as an emerging CVD risk factor but no definite causal relationship was established properly due to close association between sdLDL-C,

UNDER PEER REVIEW

triglycerides and other risk factor.[12] Small, dense LDL-C is now seen as a valuable screening and preventive tool in the assessment of CVD most especially in patients with metabolic syndrome[13] and also featuring in some clinical guidelines for the management of dyslipidaemia.[14] Prevalence of dyslipidaemia has been reported to be high in all the six geopolitical zones in Nigeria most especially reduced HDL-cholesterol and elevated LDL-cholesterol.[15] In apparently healthy and diabetic Nigerians, dyslipidaemia has been reported as high as 60% and 89% respectively. Dyslipidaemia was also documented among obese women in Southeastern Nigeria most especially elevated triglyceride, reduced HDL-cholesterol and elevated LDL-cholesterol.[34]

This study assessed the pattern of dyslipidaemia as it relates to atherogenic triad among overweight and obese adults in Benin City, Nigeria.

Materials and methods

A total of 138 subjects were recruited and categorized equally as ideal weight, overweight and obese using the National Institute of Health criteria for body mass index classification (NIH,2000). The study population consisted of male and female subjects between the ages of 18-65 years. Subjects were selected using systematic sampling method. They were recruited from clients who came for routine investigations at the Centre for Disease Control and Prevention (CDC Unit) of the Department of Community Health, UBTH, where apparently healthy individuals are routinely screened for common diseases; the Metabolic Clinic of the Department of Chemical Pathology in UBTH, where patients with metabolic diseases are evaluated and managed. The controls (ideal weight individuals) with BMI of 18.5-25.0 kg/m^2 were both male and female individuals between the ages of 18-65 years recruited from the hospital workers. Subjects currently taking lipid-lowering agents, contraceptive and other steroid were excluded. Pregnant and breastfeeding mothers were also excluded. Ethical

UNDER PEER REVIEW

clearance was obtained from the Ethical Committee of the University of Benin Teaching Hospital (ADM/E 22/A/VOL.VII/1078). Written consent was obtained from the subjects.

Height was measured (to the nearest 0.1cm) using stadiometer (*RGZ-120*) with the subjects standing erect against the wall on a horizontal floor without shoes. The head was positioned in such a way that the external auditory meatus and the angle of the eye in horizontal plane.[16]

Body mass index (BMI) was calculated as weight divided by height metre square (kg/m^2).[17] BMI of >30 kg/m^2 was considered as obese and 25-29.9 kg/m^2 as overweight while among the ideal weight controls; BMI was 18-24.9 kg/m^2. [17] Waist circumference was measured midway between the inferior margin of the last rib and the iliac crest in a horizontal plane with the measuring tape not compressing the soft tissue and subject standing with feet 25-30 cm apart to ensure the weight is evenly distributed.[18] Blood pressure (systolic and diastolic) in mmHg was measured using sphygmomanometer and Litmann® stethoscope. The blood pressure was taken using Accousson® sphygmomanometer with the subject in relaxed sitting position.[109]The cuff was wrapped round the left mid upper arm; systolic blood pressure was detected initially by palpation and later by the Korotkov sounds I and V to determine systolic and diastolic pressures respectively.

Five milliliters (5 ml) of venous blood was collected under aseptic procedure from the antecubital vein of all the subjects. Blood was dispensed into potassium ethylene diamine tetraacetic acid (EDTA) specimen bottle for fasting plasma lipids profile (FPLP) and sdLDL-cholesterol. Blood was centrifuged at 3000 revolutions per minute for 10 minutes, and plasma separated and stored in -80°C freezer not later than 2 weeks before they were analysed.

Estimation of small dense LDL-cholesterol:

Small dense LDL-Cholesterol was determined by simple precipitation method. This was done by heparin-manganese precipitation according to the method of Hirano *et al*.[19]

UNDER PEER REVIEW

121 Thirty (30) mmol/l of manganese II chloride, $MnCl_2$ was prepared by dissolving 1.485 g in
122 250 ml of distil water while 40 IU/ml sodium-heparin was prepared by adding 0.2 g of the
123 salt into 500 ml of distil water (20,000 IU in 500 ml of distil water) since 100 IU sodium–
124 heparin is equivalent to 1mg of the salt.[19]

125 **Procedure for sdLDL-cholesterol estimation**

126 1. The precipitation reagent (0.1 ml), containing 150 IU/ml heparin-sodium salt (*Elabscience*,
127 LOT: AKOO17MAY13042) and 90 mmol/L Manganese II chloride tetrahydrate (*Loba*
128 *Chemie*, LOT:L157011601) were added to each serum sample (0.1ml), mixed and incubated
129 for 10 minutes at 37^0C.

130 2. The samples were placed in an ice bath and allowed to stand for 15 minutes. This was
131 followed by centrifugation 15,000 rpm for 15 minutes at 4^0C using a cold centrifuge (*Rotina*
132 380R, Singapore).

133 3. An aliquot of the supernatant was taken for routine cholesterol analysis.

134 4. The cholesterol content was determined using enzymatic method (CHOD-PAP assay) for
135 total cholesterol as described by Allain *et al.*

136 5. Small dense LDL-Cholesterol was calculated as: sdLDL-C= Measured cholesterol - HDL-
137 C

138 Total cholesterol and triglyceride were determined using enzymatic methods[20] while HDL-
139 cholesterol was determined using precipitation method as described by Burstein *et al.*[21]
140 Calculated LDL-cholesterol was estimated using Friedewald equation[23] (LDL-C mmol/L=
141 Total cholesterol- HDL-C – triglyceride/2.2) Non-HDL-cholesterol was estimated as the
142 difference between total cholesterol and HDL-cholesterol. Control sera from Randox® (UK)
143 (levels 1 and 3) were assayed for each run. Controls and standards were analysed 10 times to

UNDER PEER REVIEW

determine the mean, standard deviation and then coefficient of variation (CV=mean/standard deviation x 100) were calculated to determine the precision. The estimated CV for the various assays were: sdLDL-C (2.1%), total cholesterol (3%), and triglyceride (4%). These CVs were in agreement with values stated by the kit manufacturers. Their precisions are: sdLDL-C (97.7%), total cholesterol (97%) and triglyceride (96%). The reference intervals for various biochemical parameters were stated as plasma sdLDL-C(0.197 – 1.347 mmol/l), total cholesterol(2.38 -4.65 mmol/l),LDL – C (1.99 – 3.36 mmol/l), HDL – C (0.75 – 1.55 mmol/l), Triglyceride (0.22 – 0.87 mmol/l).

Data analysis

Data was analysed using the Statistical Package for Social Science (SPSS) version 20 (IBM Corp., Amonk, NY; released 2011). Data were tested for normality using Kolmogrov-Smirnov test and were found to be normally distributed. Results were expressed as mean ± standard deviation; student t-test and analysis of variance (ANOVA) were used for comparison of means between two groups and multiple groups respectively. Statistical significance was set at $p < 0.05$.

Results

One hundred and thirty-eight subjects made up of 88 females and 50 males were recruited in this study. They include 46 ideal weight, 46 overweight and 46 obese. Their mean ages of 55.57 ± 10.48, 48.91 ± 8.33 and 45.11 ± 7.61 years respectively. Thirty-eight (82.6%) of the ideal weight subjects were females, 22 (47.8%) of the overweight subjects were males while 30 (65.2%) of the obese were females. Their means ages were 55.57 ± 10.48, 48.91 ± 8.33 and 45.11 ± 7.61 years respectively. Thirty-eight (82.6%) of the normal weight subject were females, 22 (47.8%) of the overweight subjects were males while 30 (65.2%) of the obese were females. There was no statistical differences in their age distribution (p=0.000). Their

UNDER PEER REVIEW

anthropometric, clinical and biochemical parameters were measured and documented in the table I.

Anthropometric and clinical parameters.

The mean weight, height, BMI, waist circumference, hip circumference and waist hip ratio are shown in Table I. Using one-way ANOVA across the 3 groups, there was a significant difference (p=0.000) in the anthropometric parameters except the height (p=0.054) of the participants. More so, there was a significant difference (p=0.000) in systolic blood pressure, respiratory and pulse rates but no difference was found in diastolic blood pressure (p=0.064).

Biochemical profile of the subjects.

The average serum total cholesterol levels across the groups were 5.68 ± 0.99, 5.36 ± 1.25 and 6.28 ± 1.05 mmol/L respectively (F=2.9; p=0.000). Serum triglyceride levels across the groups were not statistically different (p=0.354). There was reduced HDL-cholesterol among the normal weight subjects. There was no statistical difference between LDL-cholesterol levels between the normal weight and obese subject (p=0.520). Dyslipidaemia was observed across the three groups, most especially elevated LDL-cholesterol, elevated triglyceride, occurring in more than 70% of all the subjects. Elevated total cholesterol was seen in 95.7% of the obese subjects.

Highest mean values for serum total cholesterol, LDL-cholesterol and small dense LDL-cholesterol were recorded among the obese participants. Moreso, highest level of HDL-cholesterol was found among the overweight category while mean triglyceride level was the highest among the normal weight participants. The average sdLDL-cholesterol levels were found to be 0.79 ± 0.16, 0.96 ± 0.15 and 1.33 ± 0.26 mmol/l among the normal weight, overweight and obese participants respectively with a significant difference existing between the three groups (F=7.3, p=0.000). There was no significant difference in the serum levels of

UNDER PEER REVIEW

triglycerides among the groups (F=1.1; p=0.354). There was a significant difference in the means of all the biochemical parameters except serum triglyceride (p=0.354). There was no significant difference between LDL-C levels in normal weight and obese subjects (p=0.520). However, a statistically significant difference was found in sdLDL-C between normal weight and obese subjects (p=0.000). Dyslipidaemia was observed across the three groups; most especially elevated LDL-cholesterol elevated triglyceride occurring in more than 70% of all the subjects while elevated total cholesterol was seen in 95.7% of the obese subjects. Elevated sdLDL-C was seen in 10(12.7%) and 20(43.5%) of the overweight and obese subjects respectively, while atherogenic triad (a constellation of elevated triglyceride, reduced HDL-C and elevated sdLDL-cholesterol) was observed in 7(15.2%) of the obese subjects There was no statistical difference between hypertriglyceridaemia across the three groups (p=0.713) unlike other abnormalities which were statistically significant ($p<0.05$). Moreso, 2 (3.6%) of the obese subjects had elevated sdLDL-C with LDL-C within the reference interval.

Table 1: Anthropometric and Clinical characteristics of the study subjects

Variables	Ideal Weight	Overweight	Obese		
	mean ±SD	mean±SD	mean±SD	F-value	p-value
Weight (Kg)	63.3±9.48	75.54±7.78	88.93±10.65	7.6	0.000
Height (m)	1.68±1.06	1.65±0.08	1.61±0.07	1.6	0.054
BMI (Kg/m^2)	22.19±1.61	27.82±1.16	34.28±3.21	26.5	0.000
HC (cm)	86.99±10.20	98.87±7.94	98.56±15.42	4.6	0.000
WC (cm)	90.48±8.18	105.13±7.39	117.0±19.72	14.2	0.000
Age (years)	55.57±10.48	48.91±8.33	45.11±7.61	46.3	0.000
Meal frequency	2.56±0.65	2.52±0.66	2.48±0.75	1.14	0.310
SBP (mmHg)	110±9.35	137.26±19.58	132.87±18.48	4.8	0.000
DBP (mmHg)	83.26±9.74	82.0±11.50	87.87±10.07	1.6	0.004
PR (bpm)	74.±12.0	74.13±11.81	75.96±11.93	1.7	0.040

UNDER PEER REVIEW

RR (cpm)	13.35±1.34	16.17±10.33	14.3±1.40	123.4	0.000

BMI: Body mass index; WC: Waist circumference; HC: Hip – circumference; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; PR: Pulse rate; RR: Respiratory rate.

Table 2: Biochemical profile of study subjects.

Variables	Ideal Weight mean ±SD	Overweight mean±SD	Obese mean±SD	F-value	p-value
TC (mmol/L)	5.68±0.99	5.36±1.25	6.28±1.05	2.9	0.000
TG (mmol/L)	1.41±0.73	1.33±0.61	1.31±0.73	1.1	0.354
HDL-C (mmol/L)	0.85±0.20	1.05±0.34	0.94±0.30	3.2	0.000
LDL-C (mmol/L)	4.61±1.09	3.70±1.09	4.75±1.04	2.8	0.000
sdLDL-C (mmol/L)	0.79±0.16	0.96±0.15	1.33±0.26	7.3	0.000

TC: Total cholesterol; TG: Triglyceride; HDL-C: High density lipoprotein-cholesterol; LDL-C: Low density lipoprotein-cholesterol, sdLDL-C: small dense low density lipoprotein-cholesterol.

Table 3: Frequencies of elevated biochemical parameters and lipid atherogenic triad in normal weight, overweight and obese subjects.

Abnormalities	Ideal weight (n=46)	Overweight (n=46)	Obese (n=46)	χ^2	p-value
Elevated TC	40 (87%)	32 (69.6%)	44 (95.7%)	10.12	0.006
Elevated TG	35 (76.1%)	35 (76.1%)	33 (71.7%)	0.676	0.713
Elevated LDL-C	39 (84.8%)	27 (58.7%)	41 (89.1%)	20.52	0.000
Elevated sdLDL-C	0 (0%)	10 (21.7%)	20 (43.5%)	46.78	0.000
Reduced HDL-C	18 (39.1%)	7 (15.2%)	18 (39.1%)	12.31	0.000
Atherogenic triad	0 (0%)	0 (0%)	7 (15.2%)	-	-

UNDER PEER REVIEW

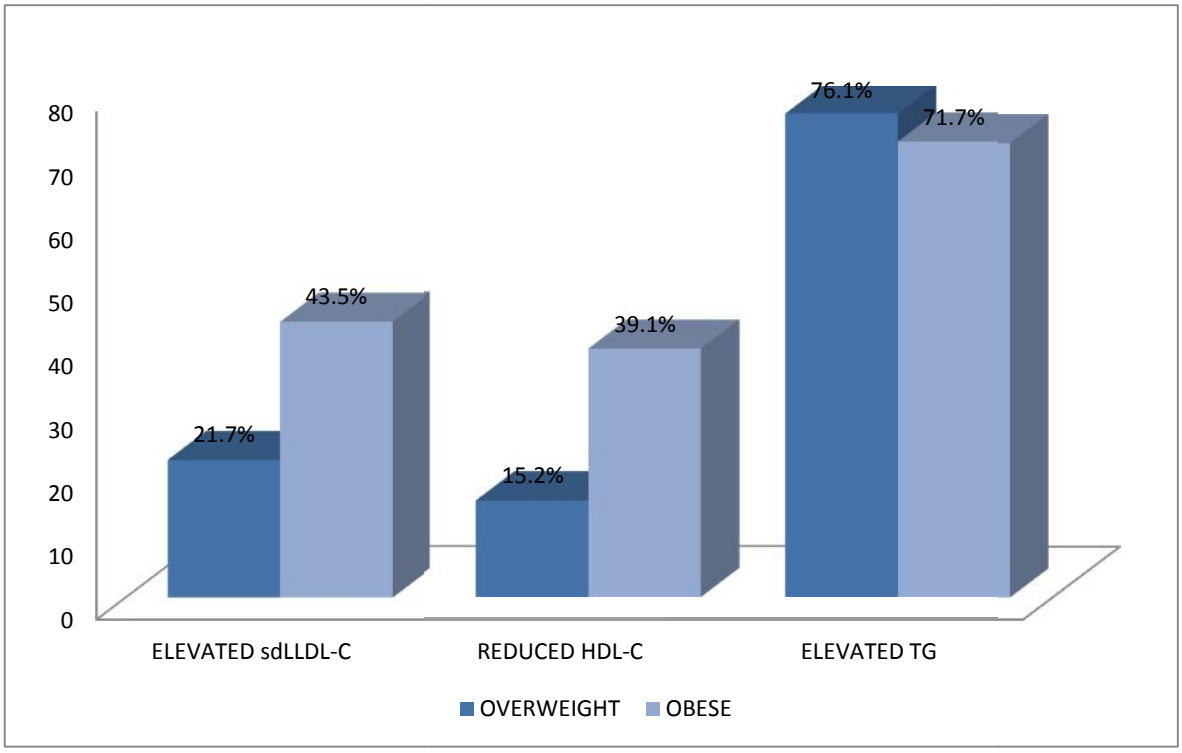

Figure 1: Prevalence of components of atherogenic triad in overweight and obese subjects.

DISCUSSION

Atherogenic triad is characterized by elevated sdLDL cholesterol, increased triglyceride and reduced HDL-cholesterol. This has been reported to be of higher clinical significance that LDL- cholesterol as atherogenic triad is commonly found in patient with coronary artery disease, diabetes mellitus, obesity and metabolic syndrome.[23] Overweight or pre-obesity is defined as having more body fat than is optimally healthy[24] while obesity is a medical condition in which excess body fat has accumulated to the extent of having a negative effect on the health of the individual.[25] Obesity arises from the combination of excessive food intake, lack of physical activity and genetic susceptibility.[26]

Atherogenic triad has been report as a feature of obesity and predisposes the obese to cardiovascular diseases.[27] Alteration in lipoprotein metabolism leads to the elevation of lipid

UNDER PEER REVIEW

231 particles rich in triglycerides remnants such as chylomicrons, very low density lipoprotein
232 (VLDL) and intermediate density lipoprotein (IDL). Like LDL, these remnant particles
233 readily penetrate the intima of arterial wall to cause atherosclerosis.[28]

234 Presence of elevated triglyceride contributes immensely to the formation[6] of sdLDL particles
235 from VLDL 1. HDL-C protects the arterial vessels from atherosclerosis as it promotes
236 reverse-cholesterol transport from cells in the vessel wall to the liver for elimination.[29]

237 This study showed that the prevalence of atherogenic triad in the obese subjects as 15.7 %.
238 This prevalence is a bit reduced from the prevalence (24.08%) reported among Germans
239 population.[29] Dietary habits among the Germans could account for higher prevalence of
240 atherogenic triad seen in their population.[29]

241 However, a lower prevalence of atherogenic triad was reported among the Spanish working
242 population.[30] Elevated sdLDL-Cholesterol has been reported as one of the additional
243 cardiovascular risk factor in most population.

244 This study observed an elevated sdLDL-C among the overweight (21.7%) and obese (43.5%)
245 subjects. The only study pointing to elevated sdLDL-Cholesterol among diabetics in Nigeria
246 was reported by Inaku *et al*; where the percentage sdLDL (%) among the diabetic patients
247 and control group were 45±17.79 and 32± 15.93% respectively.[31] Our study is also in
248 agreement with elevated sdLDL-C reported in adult Thai population. This implies that obese
249 and diabetic Nigerians are at risk of cardiovascular diseases.

250 Elevated triglyceride observed in more than seventy percent of overweight and obese in this
251 study further support the previous studies that reported prevalence of hypertriglyceridaemia
252 as 34.1% among women in South-Eastern Region, Nigeria.[32] However, Iloh *et al* reported the
253 prevalence of hypertriglyceridaemia as 4.7% among obese adult Nigerians.[33]

UNDER PEER REVIEW

The reduced HDL-C observed in this study also corroborates the findings reported by Oguejiofor *et al* who reported high prevalence of dyslipidaemia across the six geopolitical zones in Nigeria, most especially reduced HDL-cholesterol and elevated LDL-cholesterol among apparently healthy Nigerians.[15] Our study is also in agreement with reduced HDL-C levels reported by Ilo *et al* among the adult population in Nigeria.[34]

Abnormalities in blood lipids have been well reported among the overweight and obese individuals. Elevated LDL-cholesterol, triglyceride and low HDL-cholesterol are risk factors for the development of cardiovascular diseases. In this study; dyslipidaemia was observed across the three groups most especially elevated LDL-cholesterol which cut across the three groups. It was also observed that there is no significant difference between LDL-C levels in normal weight and obese subjects but a statistically significant difference seen in the sdLDL-C levels in both groups. These abnormalities may be a pointer to increased prevalence of metabolic syndrome and dyslipidaemia among normal weight, overweight and obese subjects in the larger population.

LIMITATION:

Reference interval for sdLDL-C used in the interpretation of the results is from Caucasian population as local reference interval for sdLDL-C is not available yet

CONCLUSION:

Atherogenic triad is 15.7% in the obese subjects while the prevalence of the components of atherogenic triad were high in the study population, most especially in the obese. These findings necessitate institutionalizing preventive measures such as therapeutic lifestyle modification among the overweight and obese individuals to prevent cardiovascular diseases.

UNDER PEER REVIEW

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UNDER PEER REVIEW

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UNDER PEER REVIEW

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UNDER PEER REVIEW

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UNDER PEER REVIEW

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