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ORIGINAL RESEARCH

Relationship between bone turnover markers and cardiovascular risk factors in healthy Nigerian adults

Ale AO*, Familoni OB, Ogunsemi OO, Afe TO, Adeleye OO, Adeyemo OL

Department of Medicine, Olabisi Onabanjo University/ Teaching Hospital, Sagamu, Ogun State, Nigeria

***Correspondence: Dr AO Ale, Department of Medicine, Olabisi Onabanjo University/ Teaching Hospital, Sagamu, Ogun State, Nigeria. E-mail: ayoale2004@yahoo.com; ORCID - https://orcid.org/0000-0003-1779-7311.**

Abstract

Background: Osteoporosis and cardiovascular diseases are global public health concerns. Both diseases have been linked through common risk factors and biological mechanisms.
Objective: To evaluate the association between bone turnover markers (BTM) and some cardiovascular risk factors among healthy Nigerian adults.
Methods: This was a cross-sectional, observational study of 80 healthy participants of less than 50 years of age. Clinical data were obtained through an interviewer-based questionnaire. Fasting blood samples were analysed for Osteocalcin (OC), Total Alkaline phosphatase (ALP), 25-hydroxyvitamin D (25-OHVitD), Calcium (Ca), Fasting Blood Glucose (FBG). Two-hour postprandial blood glucose (2HPP) Calcium-phosphorus product calculated (CAP) and 24-hour urinary calcium excretion (CaE) were determined.
Results: The mean age of the participants was 32.1±5.8 years, mean BMI was 26.3±4.0kg/m^2 and the mean waist circumference (WC) was 79.6±16.0cm. OC was directly correlated with ALP (r = 0.4, p = 0.006) but not with CaE (p = 0.8). Serum OC was inversely correlated with age, BMI and WC. ALP was negatively correlated with FBG (r = - 0.3, p = 0.04), 2HPP (r = - 0.65, p = 0.000). Multivariate regression showed that BTMs-OC, ALP and CAE independently predicted BMI, 2HPP, DBP and FBG respectively.
Conclusion: This study showed a relationship between bone markers and selected cardiovascular risk factors in Nigerian adults. Therefore, patients with cardiovascular disease may benefit from bone health screening or vice versa.

Keywords: Bone Turnover Markers, Calcium, Cardiovascular risk factors, Nigeria, Osteocalcin.

Introduction

Metabolic bone disease and cardiovascular disease are degenerative diseases of growing concern globally. Osteoporosis is a common bone disease characterized by low bone density, disruption of bone micro-structure leading to increased skeletal fragility, and risk of fractures particularly at the spine, hip, humerus, and pelvis. [1] Cardiovascular disease (CVD) is a group of disorders of the heart and blood vessels that could result from uncontrolled hypertension, valvular, congestive heart diseases, and coronary, peripheral, and cerebrovascular diseases respectively. [2] Studies have suggested shared pathophysiology, [3] common risk factors for both, [4] while others reported a causal linkage. [3] In healthy adults, researchers have reported linkage between the bone turnover markers (BTM) and cardiovascular risk factors (CV). This forms the template on which the inter-

relationship between both diseases was studied.

Bone is a dynamic tissue that continuously undergoes remodelling, which is a coordinated normal physiologic process of coupling of formation and resorption activities, culminating in skeletal growth, renewal, and repairs. [5] Abnormality of any or both phases leads to the uncoupling of remodelling resulting in a diseased bone. [5] Cardiovascular risk factors are key indices of metabolic dysfunction and clustering of these factors (including adiposity- overweight or obesity, elevated blood glucose, elevated blood pressure, hypercholesterolemia, or dyslipidaemia) leads to cardiovascular disease and associated complications. [6]

Bone is an endocrine organ. It synthesizes and secretes hormones involved in many metabolic processes in addition to sub-serving structural support, mobility, calcium homeostasis, and hematopoietic functions. [7] Bones are made up of specialized cells which include osteocytes, osteoblasts, osteoclasts, and chondrocytes among others. Osteoblasts synthesize bone matrix while osteoclasts secrete protons and enzymes responsible for the resorption of bone. [7]

Osteocalcin is a hormone product of osteoblasts, a marker of bone formation with extra-skeletal functions. [8] It regulates energy metabolisms, especially glucose and fat metabolisms, by stimulating insulin secretion, expression, pancreatic beta-cells proliferation, and adipocyte differentiation which increases insulin sensitivity in peripheral tissues. [9] Its other effects in the brain (cognition), testes (reproduction), and muscles (strength) have been postulated. [10] Animal studies have established a critical role of osteocalcin in bone formation, endocrine, and metabolic processes. Osteocalcin-mediated processes have been demonstrated to be linked to cardiovascular and metabolic diseases through molecular mechanisms. [11-13] However, there are very few studies to substantiate this hypothesis in humans.

Alkaline phosphatase is made up of isoenzymes, produced mainly from the liver and bone, with some produced in the intestine and kidney. [14] It denotes a bone formation marker for this study because of cost-effectiveness and availability compared to the bone-specific Alkaline phosphatase. Studies in the healthy population have shown that bone-specific ALP correlated with insulin resistance and metabolic syndrome. Also, the deleterious effect of high glucose levels on osteoblasts function and activity in-vitro studies is well researched. [15] Vitamin-D is a hormone that maintains calcium and phosphorus balance and bone health. Also, it modulates unique cell-specific biology in numerous extra-skeletal.[16] Low body vitamin-D plays a critical role in the pathogenesis of cardiovascular diseases and events. [17, 18]

Calcium excretion is the osteolytic product of bone resorption and calcium homeostasis. Twenty-four-hour calcium excretion is an established marker of bone osteoclastic activity and also, a reflection of vitamin-D/calcium-phosphorus metabolism. There are scarce reports on calcium excretion as a marker of bone resorption and its inter-relationship to cardiovascular risk factors. Some of the above -mentioned bone turnover markers - osteocalcin, Alkaline phosphatase, and vitamin D - have been reported to play a critical role in the pathophysiology of cardiovascular disease and osteoporosis.

Globally, correlation studies on BTMs and CV risk factors reported in the healthy population, [19, 20] and cardiovascular disease and events, [13,21] existed only in Caucasian and Asian populations. Further research in sub-Saharan Africa and Nigeria on the inter-relationship between BTMs and CV risk factors; and CVD and osteoporosis needs to be conducted. This study aimed to determine the correlation of biochemical bone turnover markers with some

cardiovascular risk factors among apparently healthy Nigerian adults and to create awareness among clinicians on the need to screen for both diseases simultaneously to stem the burden associated with either disease. Furthermore, this study will serve as a template for future research in the area of inter-relationship between cardiovascular and bone biology in Nigerians.

Methods

Study design

This cross-sectional study was conducted at the Endocrinology, Diabetes and Metabolism Unit of the Department of Medicine, Lagos State University Teaching Hospital (LASUTH), Ikeja, Lagos State, Nigeria between 2011 and 2013. Ethical approval for this research was obtained from the Lagos State University Hospital Ethics Committee (reference number LREC/10/06/141), and informed consent was obtained from all participants before the study commenced.

Participants

Eighty (80) healthy subjects aged 22 to <50 years participated in the study. Healthy volunteers were recruited from among the hospital staff and healthy relatives of patients who visited the hospital. Exclusion criteria included acute/chronic medical or surgical diseases, any medication use, pregnancy, and cigarette smoking or alcohol intake.

Clinical Assessments

Clinical data were collected using a structured interviewer-based questionnaire. Blood pressure was determined after 5 minutes of seated rest; the participant was placed in sitting and relaxed position and the left arm resting on a table at the same level of the heart with the appropriate-sizes cuff of Accoson® (England) mercury sphygmomanometer. The systolic and diastolic blood pressures were taken as the appearance and disappearance of Korotkoff sounds (Phases 1and V) respectively, read to the nearest 2mmHg and the average of two measurements were used in the analyses. Body weight was measured in light clothing, without shoes using a standard weighing scale, height was measured using a stadiometer while the waist circumference was measured using a non-elastic measuring tape. All the measurements were read to the closest 0.1cm via standardized protocols. The Body Mass Index (BMI) was calculated as weight (kilograms) divided by the square of height (metres^2).

Biochemical Analyses

Fasting blood samples were drawn and analysed for fasting blood glucose, alkaline phosphatase, and 2- Hour Postprandial glucose measured after a glucose load. Early morning urine was collected in the fasted state for calcium and creatinine assessment. Clinical chemistry including serum calcium, albumin, inorganic phosphorus, alkaline phosphatase, creatinine, and glucose was determined by timed-end point, Albumin-BromoCresol Green (BCG) complex method, molybdate, Hausamenetal method, modified Jaffe method, and glucose oxidase reaction methods respectively using Randox kits [22-27] and albumin adjusted serum calcium was calculated.

Hormonal Analyses

Quantitative determination of serum osteocalcin (1-43/49) and 25–hydroxyvitamin-D were performed by the Enzyme-linked immunosorbent assay (ELISA) method. ELISA kits were procured from Alpco Immunoassay (43-OSNHU-E01, LOT NO-D852), Salem, NH, and Immuno-diagnostic Systems (AC-57F1, LOT 11971), U.K respectively. The assay results were read off using a Thermo-Fisher multiscan EX microplate reader after following the manufacturer's recommended procedure.

Data Analyses

Data analyses were performed using the Statistical Package for Social Science (SPSS for Windows version 21.0 SPSS Institute, Chicago, IL, USA). Quantitative data were expressed as means and standard deviations, while qualitative data were reported as percentages. Pearson's correlation was used to determine

the association between BTM and cardiovascular risk factors. Multiple regression analysis was used to determine possible predictors of cardiovascular risk factors. *P* values less than 0.05 were regarded as statistically significant.

Results

Demographics

The mean age of the 80 participants was 32.10±5.8 years. There was no difference between the mean ages of females 34.85±6.6 years and males 35.43±6.9 years (p = 0.1). The mean values of the other clinical and biochemical characteristics of the participants are depicted in Table I.

Correlation between bone markers

Bone formation markers: Osteocalcin (OC) was positively correlated with total Alkaline Phosphatase (r = 0.43, p = 0.006). Neither OC nor Total ALP had correlation with bone resorption marker – calcium excretion in our study [(r = 0.04, p = 0.8 and r = 0.85, p = 0.6 respectively) Table II].

Correlation of bone markers with Cardiovascular Risk Factors

Osteocalcin

OC was inversely correlated with age (r = - 0.3, p = 0.035) and adiposity marker - BMI (r = - 0.43, p = 0.006). It also showed an insignificant negative trend with waist circumference (r = - 0.3, p = 0.05).

Alkaline Phosphatase

Total ALP showed an insignificant negative trend with age (r = - 0.34, p = 0.05). It was inversely correlated with glycaemic indices; Fasting Blood Glucose (FBG) (r = - 0.3, p = 0.042) and 2-Hour Postprandial Glucose (2HPP) (r = - 0.65, p = 0.000).

Calcium excretion (CaE)

Calcium excretion was inversely correlated to glycaemic index (FBG) (r = - 0.4, p = 0.015), Diastolic Blood Pressure (DBP) (r = - 0.35, p = 0.028) and 25-OHVitD (r = - 0.33, p = 0.041). An insignificant negative trend was observed with Systolic Blood Pressure (SBP) (r = - 0.3, p = 0.086) (Table III).

Correlation of Calcium-phosphate product with Bone Markers and 25-OHVitD

Table I: Mean values of clinical and biochemical parameters of the 80 subjects

Parameters	***Mean ± Standard deviation***
Age (years)	32.1±5.8
BMI (kg/m²)	26.3±4.0
Waist Circumference (cm)	79.60± 16.0
Systolic Blood Pressure (mmHg)	112.4±12.9
Diastolic Blood Pressure (mmHg)	76.0± 7.0
Fasting Blood Glucose (mg/dl)	84.9±12.6
2-Hour Postprandial Glucose (mg/dl)	106.0±14.16
Osteocalcin (ng/ml)	17.6±10.6
Alkaline phosphatase (IU/l)	70.6±16.5
Calcium excretion (mg/24hours)	397.1±101.8
Corrected Calcium (mmol/l)	2.1±0.2
Serum Calcium –phosphate (mmol/l)	3.1±0.8
Serum 25- Hydroxyvitamin D (mmol/l)	51.5±15.4
Serum Creatinine (mg/dl)	83.6±16.9
Urine Creatinine (µmol/l)	8171.5±1530.8

Table II: Correlation between bone markers and Vitamin D

	OC	*ALP*	*25-OHVitD*	*CaE*
OC	-	r = 0.43, p = 0.006**	r = -0.79, p = 0.6	r = 0.04, p = 0.8
ALP	-	-	r = -0.06, p = 0.7	r = - 0.85, p = 0.6
25 –OHVITD	-	-	-	r = - 0.33, p = 0.04*
CaE	r - 0.85, p = 0.6	-	-	-

**** Significant at 0.01**
*** Significant at 0.05**
OC - Osteocalcin; ALP - Total alkaline phosphatase; 25-OHVitD - 25Hydroxyvitamin-D; CaE - Calcium Excretion

Serum calcium-phosphorus product correlated positively with bone resorption marker - calcium excretion (r = 0.35, p = 0.025) but negatively with 25-OHVitD (r = - 0.23, p = 0.015). However it did not show any correlation with osteocalcin or Alkaline Phosphatase (p =0.72; p=0.29).

Correlation between 25-OHVit D and Cardiovascular Risk Factors

A non- significant trend was observed with age (p = 0.075) and WC (p = 0.08). There was no correlation between serum vitamin-D and BMI (p = 0.6), SBP (p = 0.21), DBP (p = 0.5) and glycaemic indices: FBG (p = 0.27, 2HPP (P = 0.22) as shown in Table III.

Table III: Correlation of bone markers with cardiovascular risk factors and Calcium-Phosphorus product

Factors	*OC* *r ; p*	*P* *r; p*	*25-OHVITD* *r; p*	*CaE* *r; p*
Age	-0.334; 0.035	-0.311; 0.051	0.3; 0.075	-0.31; 0.4
BMI	-0.43; 0.006	-0.255; 0.112	-0.8; 0.6	-0.2; 0.5
WC	-0.31; 0.05	-0.081; -0.621	0.3; 0.08	-0.17; 0.3
SBP	0.062; 0.72	-0.155; 0.341	0.2; 0.21	-0.28; 0.086
DBP	0.193; 0.23	-0.027; 0.868	-0.12; 0.5	-0.35; 0.03
FBG	-0.08; 0.63	-0.323; 0.042	0.2; 0.27	-0.38; 0.01
2HPP	-0.12; 0.47	-0.649; 0.000	0.2; 0.22	-0.12; 0.45
Corrected Calcium	0.11; 0.946	0.100; 0.540	0.065; 0.692	-0.103; 0.527
CAP	0.059; 0.716	0.173; 0.287	-0.23; 0.015	0.35; 0.025

r - Correlation Coefficient; p - Level of statistical significance
BMI -Body Mass Index; WC - Waist Circumference; SBP - Systolic Blood Pressure;
DBP - Diastolic Blood Pressure; 2HPP - 2- Hour Postprandial; CAP - Calcium-phosphorus product.

Regression Analysis

Osteocalcin

The outcome of a multivariate regression analysis of all cardiovascular risk factors showed that osteocalcin independently predicted BMI (adjusted OR = -2.3; 95% CI = -0.27 - 0.20). An individual with low osteocalcin was two times more likely to be overweight or obese (Table IV). Osteocalcin showed a non-significant trend with WC (p = 0.072), FBS (p = 0.09) and DBP (p = 0.09) (Table IV). Other parameters had non-significant associations and trends: age (p = 0.19), SBP (p = 0.28), 2HPP (p = 0.11), CAP (p = 0.46) (Table IV).

Table IV: Multivariate predictors of Bone Turnover Markers

	B	*Adjusted OR*	*95% C.I Lower*	*Upper*	*p-value*
Serum OC					
BMI	-0.388	-2.345	-0.272	-0.20	0.025
WC	-0.317	-1.856	-1.062	0.047	0.072
FBS	-0.268	-1.744	-0.686	0.052	0.090
DBP	0.276	1.694	-0.036	0.401	0.090
Other CV risk factors	-				>0.05
Serum ALP					
2-HPP	0.749	-5.635	-0.871	-0.410	<0.001
Other CV risk factors					>0.05
Serum 25-OHVitD					
All CV risk factors					>0.05
CaE					
FBS	-0.348	-2.614	-0.085	-0.011	0.013
DBP	0.459	-2.936	0.054	-0.010	0.006
CAP	0.287	1.753	0.000	0.005	0.088
All CV risk factors					>0.05

Alkaline Phosphatase (ALP)

ALP was a strong predictor of 2-Hour Postprandial Glucose (2HPP) (adjusted OR = –5.63; 95% CI = -7.87 to 0. 41; p < 0.001) of all the cardiovascular risk factors. An individual with low ALP was five times more likely to have elevated 2-Hour Postprandial Glucose. Other parameters had non-significant associations and trends: age (p = 0.23), BMI (p = 0.51), WC (p = 0.72), SBP (p = 0.16), DBP (p = 0.23), FBS (p = 0.13) and CAP (p = 0.23) (Table IV).

Vitamin D

Vitamin D was not a likely predictor of any cardiovascular risk factors (age (p = 0.15), BMI (p = 0.29), WC (p = 0.17), SBP (p = 0.48), DBP (p = 0.11), FBS (p = 0.90), 2HPP (p = 0.35) and CAP (p = 0.41) (Table IV).

Calcium Excretion

CaE was the strongest predictor of DBP (adjusted OR = -2.93; 95% CI = -3.05 to 0.01; p = 0.006) followed by FBS (adjusted OR = -2.61, 95% CI = -3.08 to -0.01; p = 0.013). This implies that an individual with low calcium excretion is 2.9 times and 2.6 times respectively more likely to have elevated DBP and FBG. CaE showed a non-significant trend with CAP (p = 0.088). Other cardiovascular parameters had non-significant associations and trends: age (p = 0.72), BMI (p = 0.36), WC (p = 0.64) and SBP (p = 0.12) (Table IV).

Discussion

There are few reports on the association of bone markers and cardiovascular risk factors in healthy adults and majority were conducted in older age groups, elderly and only a report in early young adulthood (17-22 years) and young adults (32-34 years) documented in the literature. [19, 20] Therefore, the present study focused on the age group of 22-50 years (mean age of 32.1 years) who had attained skeletal maturity and 95% of peak bone mass was present and only a few risk factors for CVD may have emerged. [20]

The findings in the present study showed an inverse association between bone health markers and some cardiovascular risks factors; and possible predictors of cardiovascular risk factors. Also, to the knowledge of the authors of this study, this is the first study to establish

an association between bone resorption marker-calcium excretion and cardiovascular risk factors- to DBP, FBG, and a trend with SBP and vitamin-D. The inverse correlation between osteocalcin and age may be a reflection of age-related changes observed with osteocalcin. [28] OC also correlated negatively with adiposity index such as BMI but had a non-significant trend with waist circumference – a marker of central obesity. This is similar to the observations of another study which showed an inverse association between osteocalcin and BMI, waist circumference in healthy young adults. [19] Also, other pieces of evidence from systematic review and meta-analysis on osteocalcin confirmed the observation in the present study. [29] Human and animal studies have documented low OC in glucose intolerance, insulin resistance, increased adiposity and various disease conditions, osteoporosis therapy and hypertension. [8, 9] Two mechanisms of OC actions have been postulated: either through a direct or indirect effect. Stimulation of the B-cell function and increasing insulin sensitivity is a direct role of OC. An indirect effect occurs through increased blood glucose levels that suppress bone turnover and increase fat mass, increase insulin resistance, reduce adiponectin levels and increase leptins levels with attendant deleterious effects on osteoblasts. [8, 9]

Total Alkaline Phosphatase (ALP) correlated positively with osteocalcin but inversely with glycaemic indices. A non-significant negative trend with age was also observed. There are scarce data on the correlation between ALP and CV risks in literature. However, few data existed on bone alkaline phosphatase, which shows a negative correlation with CV risks. [30, 31] The findings in the present study confirmed similar observations. Alkaline phosphatase level varies with age in healthy individuals and lower levels are found in the 15-50 year age group in contrast to childhood, puberty and old age. The deleterious effect of high glucose level inhibiting osteoblastic activity can explain this observation. [14] Although ALP is a bone and hepato-biliary marker, the suppressive effect of high glucose level on the bone cannot be overlooked since co-founding factors are minimized or eliminated by excluding participants with evidence of liver, gastrointestinal and kidney disease from this study. The correlation between the OC and ALP, both as bone formation markers; and the associations with CV risk factors and insulin resistance could explain this relationship.

CaE showed an inverse relationship to 25-hydroxyvitamin D. Vitamin D plays a critical role in bone remodelling as a stimulator of bone resorption. [32] Vitamin D deficient state favours excessive osteoclastic activity resulting in bone demineralization with a tendency to hypercalcaemia. This promotes calcium–phosphate complex formation, thereby serving as a nidus for vascular calcification, and cardiovascular disease. [33] From the findings in the present study, vitamin D was inversely correlated with the calcium-phosphorus product. This may be evidence that vitamin D is an indicator of CV risk. This further confirmed the report of other studies suggesting that low vitamin D is a risk for cardiovascular disease and events. [17, 18] In addition to these findings, evidence has shown that serum calcium, either directly or indirectly, is linked to circulating lipids, glucose metabolism, BMI and blood pressure, [34] Summarily, this suggests that the tendency to hypercalcaemia promotes hypertension, hypercholesterolaemia, atherosclerosis, and dysglycaemia. A Nigeria study has reported a high prevalence of vitamin D insufficiency (70%). [35] Therefore, it can be postulated that the probability of CVD might be high in Nigeria, given the role of vitamin D in the pathogenesis of cardiovascular diseases.

Abnormal calcium excretion was inversely related to DBP, FBG but had a non-significant trend with SBP. Calcium excretion is a reflection of calcium balance and abnormal calcium levels have been linked to

cardiovascular and metabolic diseases. The tendency to hypercalcaemia may probably explain the link to high blood pressure and other CV risk factors. This is in contrast to the many studies that reported no association between bone resorption markers and cardiovascular risk factors. [31] This difference may be adduced to the different bone resorption markers studied. The present study measured calcium excretion as a resorption marker whereas other studies used amino- and carboxy-terminal cross-linked telopeptides of collagen type 1 as investigative markers.

According to the findings in this research, bone turnover markers are independent predictors of body mass index, fasting blood glucose, 2-Hour Postprandial glucose and blood pressure. This agrees with the report of possible interaction between the bone, pancreas and adipose tissue. [9] Clustering of these cardiovascular risk factors is linked to cardiovascular diseases. The role of osteocalcin in bone formation activity, endocrine and metabolic processes can be adduced from the findings in this study, and its correlation with alkaline phosphatase drive the evidence of this plausible explanation. Calcium excretion may be linked to hypercalcaemia and the propensity for calcium-phosphate complex formation may lead to vascular calcification and invariably high blood pressure and metabolic dysfunction. [33]

Some of the findings in the present study agreed with previous reports of links between osteocalcin, alkaline phosphatase and vitamin D - Calcium –phosphorus complex. However, contrary to the report in many studies, the present study found an association between bone resorption marker, calcium excretion and some cardiovascular risk factors. From the aforementioned, bone biomarkers and cardiovascular risk factors are linked in healthy young Nigerians. Alterations in bone formation and resorption activities may contribute to metabolic bone disease and/or cardiovascular disease. Therefore, it can be postulated that metabolic bone disease and cardiovascular disease may be linked. Further research is required to expatiate on this interrelationship among blacks.

This is the first research in sub-Saharan Africa and Nigeria to correlate bone markers and CV risk factors in healthy adults. Globally, there are few studies in healthy adults as most of the existing studies involved the elderly. Therefore, the present study provided reliable information on predictors, correlation of bone markers and CV risk factors in healthy adults. In a resource-limited setting like Nigeria, population studies are required to further validate the usefulness of calcium excretion and total alkaline phosphatase as bone biochemical screening tools since they are easily available and are cheaper alternatives to bone markers like osteocalcin, bone-specific Alkaline phosphatase and Dual-energy Absorptiometry (DXA) which are expensive and not readily accessible.

A limitation to this study is that the scope did not include lipidaemic indices, serum insulin, and Dual-energy Absorptiometry (DXA)-derived assessment of body composition, a reliable means of body adiposity determination and the study population is relatively small.

Conclusion

The present study found an association between bone markers and cardiovascular risk factors in Nigerian adults. OC and ALP levels correlated with age, the degree of glycaemic and adiposity. Calcium excretion correlated with vitamin-D, blood pressure and degree of fasting glycaemia while the BTMs independently predicted BMI, FBS, 2HPP and DBP.

Future research is needed to examine the inter-relationship between bone markers and

cardiovascular disease and events in the Nigerian population.

Authors' Contributions: AAO conceived and designed the study. AAO, FOB and AOL participated in data acquisition and analyses. FOB participated in the literature review. AAO, AOL, FOB, OTA and AOO participated in the drafting of the manuscript. All the authors approved the final version of the manuscript.
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