Carotid Intima-Media Thickness and Carotid Plaque: A Pilot Study of Risk Factors in an Indigenous Nigerian Population

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Background: Risk factors for carotid intima-media thickness (cIMT) and carotid plaque (CP) differ by ethnicity; however, this is not well understood in some ethnic populations. This work examines the risk factors for cIMT and CP in an indigenous Nigerian population. *Methods:* We assessed cIMT and CP in 122 participants and then performed biochemical analysis: fasting blood glucose (FBG), hemoglobin A1c, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglyceride (TG), and total cholesterol (TC). The clinical history and anthropometric characteristics of participants were recorded. Linear models were used to assess the factors associated with cIMT and CP, and stepwise multivariate regression analyses were conducted to assess the predictors of cIMT and CP. *Results:* The cIMT thickness varied from .5 mm to 1.3 mm. Family history of heart disease (FHHDx), physical activity, FBG, HDL-C, TG, TC, body mass index (BMI), systolic pressure, and waist circumference were significantly associated with cIMT ($P \leq .01$). High systolic ($\beta = .008$) and diastolic ($\beta = .17$) pressure, FHHDx ($\beta = .24$), age ($\beta = .004$), physical activity ($\beta = -.09$), and waist circumference ($\beta = -.017$) significantly predicted 85% of the variation in cIMT ($P < .001$ for all). Family history of hypertension (FHH), LDL-C, and high blood pressure were significantly associated with CP ($P \leq .05$). The significant predictors of CP were FHH ($\beta = .145$, $P = .03$), smoking ($\beta = .167$, $P = .01$), HDL-C ($\beta = .283$, $P < .001$), weight ($\beta = .150$, $P = .04$), and BMI ($\beta = .183$, $P = .01$), explaining most of the 43.2% variation in CP. *Conclusions:* Some of the risk factors differ from those of other ethnicities, suggesting a need for population-specific approach to risk assessment and early detection of subclinical disease.

Key Words: Cardiovascular disease—atherosclerosis—Nigeria—stroke—risk factors—risk prediction

Introduction

Cardiovascular disease (CVD) has been recognized as the leading cause of deaths within the last 2 decades.[1,2] Evidence shows that about 18 million deaths (31%) in 2015 were due to CVD, with 75% of these deaths occurring in the developing low- and middle income countries.[3] According to the World Health Organization, CVDs such as stroke and ischemic heart disease are the leading cause of CVD-related mortality, and accounted for over 15 million deaths worldwide over the last 2 years.[3] More concerning is the fact that there is an increasing trend in CVDs among the young population in the developing world due to lifestyle factors.[4] One of the key determinants of CVD is atherosclerosis, a condition characterized by the narrowing and stiffening of inner arterial walls.[5]

Two major factors linked to atherosclerosis are increased carotid intima-media thickness (cIMT) and carotid plaque (CP).[6] Chronic CP may cause arterial wall rupture and narrowing of arterial lumen, which compromises blood flow to the brain, leading to stroke and transitory ischemic attack.[7] Stroke, in particular, is a common cause of death in Africa, with a 2-fold increased incidence rate in the black population compared to Caucasians.[8] In Nigeria and across Africa,

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the crude prevalence of stroke has increased by 18.2% within a 9-year period.[9-11] Unfortunately, stroke-related mortality rate is considerable, ranging from 40% to 50%,[9] with postischemic stroke complications accounting for 30%-50% of these deaths,[12] significantly higher than that reported in the developed world.[13] These worrying statistics are in part related to a lack of awareness of the risk factors for stroke, and tools and expertise to manage acute stroke.[14] Given the poor economic status of this population, it is important to identify the risk factors so that economically appropriate preventive and early treatment strategies can be transformed.

The determinants of cIMT and CP are inter-related and interdependent, and include diabetes mellitus, sex, smoking, high blood pressure, physical activity, alcohol intake, diet, obesity, and race.[15-17] Other established risk factors include dyslipidemia and genetic signatures.[18,19] A majority of these risk factors are controllable and modify the relationship between other uncontrollable risk factors such as race, sex, and genetic parameters with cIMT and CP.[20] Improved understanding of these risk factors and early treatment of subclinical disease have been shown to reduce mortality.[21] However, risk factors for CVDs vary by ethnicity,[22] emphasizing the need to explore the predictors of cIMT and CP in each ethnic population so that therapeutic and ancillary preventive strategies can be better targeted.[14,23,24]

The need to identify signs of impending CVDs in each population is highlighted by the Multi-Ethnic Study of Atherosclerosis[25] and the English Longitudinal Study of Ageing.[26] Evidence from these studies has supported policy and clinical decision-making to transform population health. A few studies have assessed the correlation between comorbidities such as hypertension and diabetes mellitus with cIMT and CP in a Nigerian population,[27-30] or the correlation between anthropometric or cardiovascular parameters with cIMT and CP.[28,29] However, there is no established model for predicting cIMT and CP, the subclinical indicators of stroke and ischemic heart disease in a Nigeria population. We urgently need to address these gaps so that economically viable preventive and early treatment strategies can be effectively transformed to improve the cardiovascular health of this population. Therefore, the current work aims to examine the risk factors for cIMT and CP in an indigenous Nigerian population. This pilot work is significant since it will inform optimal health policy around early detection of signs of impending stroke and optimizes prevention and treatment of subclinical cardiovascular disease.

Materials and Methods

Study Participants

Institutional review board of the University of Benin Teaching Hospital provided ethics approval. Participants consisted of patients seeking medical services at the endocrine unit of the outpatient department and healthy individuals attending the screening clinic of the center for disease control in the same hospital. Study participants were aged 40-77 years; only those who provided informed oral consent (n = 122) were recruited for the study. Pregnant women, individuals younger than 40 years, and those who did not provide consent were excluded. For each participant, we collected demographic data and clinical information face to face using a survey sheet.

Assessment of Risk Factors for cIMT and CP

A survey sheet was developed to ensure consistency of data collection. The survey sheet sought to extract information such as age, sex, physical activity, history of hypertension and duration of hypertension, smoking status, alcohol consumption, history of diabetes mellitus, family history of heart disease (FHHDx), and a personal history of transient ischemic attack. Each of the participants was interviewed and their responses were recorded.

Physical and Laboratory Examination

The weight and height of each participant was measured and used to calculate body mass index (BMI) as a ratio of their weight (kg) and height (m^2). We also measured the waist and hip circumference of each participant; these were used to calculate their waist-to-hip ratio, and their blood pressure was also measured. Each of the participants was asked to return to the hospital on a fast so that blood samples for biochemical evaluation of fasting blood glucose (FBG) and glycosylated hemoglobin can be collected. For each participant, we measured their FBG, hemoglobin A1c, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglyceride, and total cholesterol within 12 hours after sample collection. FBG was measured within 2 hours after sample was collected. All laboratory investigations were performed in the University of Benin Teaching Hospital. The American "Association of Clinical Endocrinologists and American College of Endocrinology (AACE) 2017 clinical practice guidelines[31] and clinical practice guidelines for developing a diabetes mellitus comprehensive care plan 2015"[32] were used to select cut-off values for dyslipidemia and diabetes. Blood pressure was assessed based on the American Heart Association guidelines.[33] Physical activity was defined as brisk walk for 30 minutes at least 3 times per week.

Sonographic Evaluation of the Extracranial Carotid Arteries

Ultrasound assessment was performed using a Sonace x6 (Medison Inc, Seoul, South Korea) ultrasound machine, with a 7.5-10 MHz linear transducer. A single experienced radiologist, blinded to patients' clinical history and laboratory findings performed the ultrasound examination. Scans were performed in the supine position and the head extended and rotated away from the

side of the examination. A sand bag was placed under the shoulder of the patient to ensure stability of the neck and coupling gel applied on the anterolateral aspect of the neck.

The cIMT was measured along the arterial far wall of the 3 main segments (common carotid artery at 1-1.5 cm proximal to the carotid bulb, carotid bulb, and internal carotid artery) for each of the extracranial arteries bilaterally. The distance between the inner and outer echogenic lines, representing the intima-blood interface and adventitia-media junction, respectively, was used to define the cIMT. For this study, the right carotid artery was used, and measurements were made in the longitudinal plane. Three measurements were taken at the segments described above, and the mean value was used to represent the cIMT for that participant. The right and left extracranial carotid arteries were then screened for plaques in longitudinal and transverse sections. Normal cIMT values were defined as described by Randrianarisoa et al[34] and plaque was confirmed by the presence of at least 1 solid echogenic or hypoechoic lesion on the internal wall of one of the extracranial carotid arteries.

Statistical Analysis

The Statistical Package for the Social Sciences (IBM Corporation, Armonk, New York, United States) version 22.0 was used for all data analyses. Multivariate linear regression analyses were performed with a Fisher's least significant difference post hoc correction to assess the association between the factors above and both cIMT and CP. Stepwise multivariate regression analyses were performed to generate models for predicting cIMT and CP. Each of these models was built using all the factors described above. History of transient ischemic attack was excluded from the final analysis, as many participants did not provide such data. A 2-tailed P value $\leq .05$ was considered statistically significant.

Results

Ages of the population ranged from 40 to 77 years. A majority of the participants was female (n = 86 of 122). The cIMT thickness ranged from .5 mm to 1.3 mm. There was no difference in the mean cIMT of males and females (males: .75 ± .15; females: .74 ± .15; F = .93, P = .53). The mean cIMT was .98 mm and .68 mm for participants with high and normal cIMT, respectively. A summary of the

Table 1. *Characteristics of the population and their association with carotid intima-media thickness*

Predictors	High cIMT group (mean = .98)	Normal cIMT group (mean = .68)	F	P value
Categorical variables				
Sex: Male	23.1	13.2	.514	.73
Female	76.9	86.8		
Family history of heart disease: Yes	61.5	25	4.259	.004*
No	39.5	75		
Family history of hypertension: Yes	63.6	14.6	1.95	.11
No	36.4	85.4		
Smoking: Yes	84.6	11.5	1.275	.29
No	15.4	88.5		
Alcohol: Yes	84.6	32.3	1.180	.32
No	15.4	67.7		
Physical activity: Yes	38.5	59.4	4.024	.005*
No	61.5	40.6		
Continuous variables (mean ± SD)				
Age (years)	54.2 ± 8.6	52.7 ± 8.1	1.152	.34
Fasting blood glucose (mmol/L)	7.7 ± 2.3	6.1 ± 3.6	3.250	.01*
Hemoglobin A1c (%)	8.5 ± 3.1	6.5 ± 2.3	1.635	.18
Low-density lipoprotein-C (mg/dL)	3.5 ± 3.8	6.0 ± 3.4	1.389	.25
High-density lipoprotein-C (mg/dL)	75.3 ± 42.6	55.9 ± 36.9	3.367	.01*
Triglyceride (mmol/L)	5.9 ± 4.4	6.2 ± 3.1	2.832	.03*
Total cholesterol (mmol/L)	8.0 ± 4.9	7.9 ± 4.4	3.061	.02*
Weight (kg)	63.9 ± 11.1	70.6 ± 13.3	2.321	.06*
Height (cm)	161.2 ± 9.1	166.2 ± 8.3	.626	.65
Body mass index (kg/m^2)	24.8 ± 5.4	25.6 ± 4.5	2.873	.02*
Systolic (mmHg)	127 ± 14.6	121 ± 11.7	7.057	<.001*
Diastolic (mmHg)	75.6 ± 9.9	76.2 ± 9.2	1.785	.14
Waist circumference (cm)	91.6 ± 15.2	88.7 ± 11.3	4.009	.006*
Hip circumference (cm)	97.5 ± 13.3	101 ± 16.4	.587	.67
Waist-to-hip ratio (cm)	.95 ± .12	.95 ± .86	.299	.87

Abbreviations: cIMT, carotid intima-media thickness; F, F ratio; SD, standard deviation.
*Statistically significant.

Table 2. *Predictors of carotid intima-media thickness*

Predictor	Beta	t score	*P* value
Diastolic	.17	10.42	<.001
Family history of heart disease	.236	10.36	<.001
Age	.004	4.90	<.001
Physical activity	−.087	−5.69	<.001
Waist circumference	−.017	−8.47	<.001
Systolic pressure	.008	7.93	<.001

R = .93; R^2 = .867; adjusted R^2 = .849; standard error = .59; Durbin Watson test = 1.223.

characteristics of the study population and their association with cIMT is presented in Table 1.

Multivariate linear models showed that the factors included in the model (Table 1) are significant contributors to cIMT (value = 1.92; F = 2.28; $P < .001$). The results of univariate analysis presented in Table 1 show that FHHDx ($P = .004$), physical activity ($P = .005$), FBG ($P = .01$), HDL-C ($P = .01$), triglyceride ($P = .03$), total cholesterol ($P = .02$), BMI ($P = .02$), systolic pressure ($P < .001$), and waist circumference ($P = .006$) are statistically significantly associated with cIMT. The regression model showing the beta coefficients for predicting cIMT is presented in Table 2. The resulting model successfully predicted 85% of the variation in cIMT (R^2 = .87; adjusted R^2 = .85; standard error = .59).

Table 3 shows the characteristics of the population with and without carotid plaque. Multivariate linear models showed a statistically significant association between the factors assessed and CP (value = .62; F = 7.69; $P < .001$). Findings from the univariate analysis are presented in Table 3, and show that family history of hypertension (FHH; $P = .05$), LDL-C ($P < .001$), systolic pressure ($P < .001$), and diastolic pressure ($P = .002$) are statistically significantly associated with CP.

The regression model showing the predictors of CP and the contribution of each factor to the model are presented in Table 4. This model successfully predicted 42.3% of the variation in CP (R^2 = .438; adjusted R^2 = .423; standard error = .24). Five factors FHH (β = .145, $P = .03$), smoking (β = .167, $P = .01$), HDL-C (β = .283, $P < .001$), weight (β = .150, $P = .04$), and BMI (β = .183, $P = .01$) emerged as the most powerful and significant predictors of CP (Table 4).

Table 3. *Characteristics of the participants and their association with carotid plaque*

Predictors	Plaque	No plaque	F value	*P* value
Categorical variables				
Sex: Male	40	29.6	.289	.59
Female	60	70.4		
Family history of heart disease: Yes	21.4	22.2	.001	.9
No	78.6	77.8		
Family history of hypertension: Yes	45.1	15.7	3.91	.05*
No	54.9	84.3		
Smoking: Yes	28.6	11.1	2.85	.09
No	71.4	88.9		
Alcohol: Yes	42.9	29.6	1.0	.32
No	57.1	70.4		
Physical activity: Yes	48.2	49.2	.128	.72
No	51.8	50.8		
Continuous variables (mean ± SD)				
Age (years)	48.9 ± 8.6	41.8 ± 14.3	3.26	.07
Fasting blood glucose (mmol/L)	8.13 ± 2.3	7.34 ± 1.6	.146	.70
Hemoglobin A1c (%)	9.45 ± 3.4	10.52 ± 18.2	.047	.82
Low-density lipoprotein-C (mg/dL)	6.5 ± 3.2	5.48 ± 35.9	25.14	<.001*
High-density lipoprotein-C (mg/dL)	41.86 ± 22.45	60.75 ± 38.8	3.17	.07
Triglyceride (mmol/L)	14.8 ± 8.1	11.57 ± 17	.39	.53
Total cholesterol (mmol/L)	10.71 ± 4.9	10.62 ± 4.9	.004	.95
Weight (kg)	69.5 ± 13.5	65.14 ± 9.7	1.39	.24
Height (cm)	163.9 ± 8.5	165.32 ± 8.7	.352	.55
Body mass index (kg/m^2)	25.5 ± 4.7	24.4 ± 4.4	.613	.44
Systolic (mmHg)	135.4 ± 16.8	117.9 ± 8.9	38.1	<.001*
Diastolic (mmHg)	82.8 ± 18.9	73.5 ± 8.5	10.248	.002*
Waist circumference (cm)	93.1 ± 11.2	88.9 ± 12.3	1.445	.32
Hip circumference (cm)	97.1 ± 14.3	100.4 ± 15.8	.535	.46
Waist-to-hip ratio (cm)	.98 ± .24	.95 ± .80	.023	.88

Abbreviation: SD, standard deviation.
*Statistically significant.

Table 4. *Model for predicting carotid plaque*

Predictors	Beta	t score	*P* value
Age	.124	1.592	.11
Sex	.047	.656	.51
Family history of hypertension	.145	2.115	.03*
Smoking	.167	2.464	.01*
Alcohol	.042	.579	.56
Physical activity	.088	1.248	.22
Family history of heart disease	.024	.345	.73
Fasting blood glucose (mmol/L)	−.021	−.296	.76
Hemoglobin A1 (%)	.029	.408	.68
High-density lipoprotein (mg/dL)	.283	3.620	<.001*
Triglyceride (mmol/L)	.013	.191	.85
Weight (kg)	.150	2.062	.04*
Height (cm)	−.052	−.732	.46
Body mass index (kg/m^2)	.183	2.543	.01*
Diastolic pressure (mmHg)	.004	.049	.96
Waist circumference (mmHg)	−.007	−.097	.92
Hip circumference (cm)	.071	.998	.32
Waist-to-hip ratio (cm)	.003	.046	.96

*Statistically significant.

Discussion

A better understanding of the determinants of stroke in the Nigerian population is crucial to the optimization of preventive and early treatment strategies, particularly given the high mortality from the disease or post-treatment complications.[9,12] We report for the first time the factors associated with cIMT and CP in an indigenous Nigerian cohort and the key predictors of these 2 determinants of stroke. Our findings show that most of the risk factors for cIMT in our cohort are similar to those reported for other ethnic populations.[15-17] For example, previous studies involving Asians, Europeans, African-Americans, and Congolese have also shown that high cIMT is associated with diabetes mellitus,[15-17] high levels of LDL-C, low levels of HDL-C, and HDL/LDL-C ratio and total cholesterol,[35,36] smoking, and alcohol intake.[19,37,38] Consistent with our findings, previous studies have also reported both systolic and diastolic blood pressure as important markers of cIMT.[39,40] However, we found interesting differences between the Nigerian population and both Asians and Europeans. While anthropometric characteristics such as height, weight, BMI, waist circumference, and waist-to-hip ratio were shown to increase cIMT of Asians and Europeans,[19] only waist circumference reached statistical significance in our study. Also, we found no significant associations between cIMT and factors such as alcohol intake and smoking.

Contrary to studies in other populations reporting higher cIMT for males compared to females,[15-17] no gender-related significant differences were observed in our work. These differences may be explained by both genetic and racial differences between our study cohort and other ethnic populations. A recent review[19] supports our findings that no significant difference exists between the cIMT of males and females of Asian and European decent after adjustment for carotid diameter. Thus, for the first time, our work provides a model for predicting cIMT in a Nigerian population (Table 2). Our model successfully predicted 85% of the variation in cIMT, and suggests that blood pressure, FHHDx, age, physical activity, and waist circumference are the key significant predictors of high cIMT in this population. The model however revealed an unexpected finding that a 1-unit decrease in waist circumference significantly increased cIMT by 1.7%. This unexpected finding needs to be confirmed and explained using a larger participant cohort.

Similar to cIMT, we found similarities and differences in risk factors for CP between our cohort and ethnic populations such as Chinese,[41] Korean,[42] and Icelander.[43] Notable differences were the lack of significant association between CP and factors such as alcohol and BMI in our cohort; however, these have shown an inverse relationship with plaque in Chinese.[41] In fact, univariate linear models demonstrated no statistically significant association between carotid plaque and the anthropometric characteristics of our cohort; however, weight and BMI emerged as 2 of the significant predictors of CP, contributing 15% and 18%, respectively, to the model. High levels of LDL-C have been reported as a strong predictor of CP[41] and were also the strongest (28.3%) predictor of CP in our model. There is evidence that genetic signatures and lifestyle factors account for a significant number of carotid plaque,[18,19] and may be responsible for the small differences in our work and studies involving other ethnic population. These subtle variations in the determinants of CP may impact

differently on the risk of stroke. It is important that these differences are taken into consideration while modeling risk and preventive strategies for each population. As stated previously, there is currently no model for predicting the risk of high cIMT and CP in the Nigerian population. Therefore, our models, which successfully predicted 85% and 42.3% of cIMT and CP respectively, could be used to inform risk assessment in this population.

The findings above have significant implications for policy and practice: first, it emphasizes that patients with high blood pressure and individuals with an FHHDx, and physically inactive adults may need to be monitored for subclinical indicators of impending ischemic heart disease and stroke such as cIMT. In addition, smokers and individuals with an FHH, and high levels of LDL-C, and BMI may benefit from plaque screening. Thus, the models provided in the current work should be helpful in tailoring appropriate risk assessment, early detection, and preventive and therapeutic interventions to mitigate the risk of stroke in the Nigerian population. Early detection and treatment of subclinical disease should be tailored around the most potent risk factors to maximize the cost-benefits of such intervention given the poor economic status of this population. Finally, the similarity in cIMT between women and men has significant implication for risk stratification, and should be taken into account while generating gender-based risk profiles from cIMT.

The high mortality rates from stroke and the lack of expertise to effectively treat the disease in Nigeria emphasize the need for effective population education, and early detection and treatment of subclinical CVD. There is a general belief among the African population that acute stroke and transient ischemic attack have spiritual links,[44] and <20% of the highly educated population have any knowledge of CVDs risk factors.[45,46] If we could increase awareness of stroke and ischemic heart disease and the risk factors identified in the current work, we could reduce the myths around these diseases and facilitate the utilization of early detection and treatment services. Early detection of subclinical disease may enable economically viable preventive and early treatment strategies to be transformed to improve outcomes for individuals at risk. Finally, the work suggests that control of blood pressure, dyslipidemia, weight, and BMI may be an important strategy to mitigate cIMT and CP, the 2 important determinants of stroke. The outcomes of our work should be helpful in transforming early detection and treatment of subclinical indicators of ischemic heart disease and stroke according to the American Association of Clinical Endocrinologists guidelines.[24,31]

Our work is not without limitations: first, the sample size is relatively small, with a significantly higher female-to-male ratio; this is a pilot study and the high cost of biochemical analyses limited our ability to recruit a large number of participants. However, the data does provide preliminary evidence for selecting individuals who may benefit from early preventive and treatment interventions. Second, we employed a simple incidental sampling technique, which may have introduced some selection bias. Lastly, it has been shown that genetic parameters influence cIMT and CP[19,47]; however, these were not accounted for in the current work. Nonetheless, until sufficiently powered studies are available, our pilot data does provide models to build upon to change the current status quo around stroke and ischemic heart disease in this grossly understudied and underserved population. It therefore offers substantial opportunities for effective assessment and communication of risk, heightened surveillance, effective prevention, and early detection and treatment. The work should inform the direction and educational strategies for risk assessment in the healthy population and management of those with subclinical cardiovascular disease.

Conclusion

Some of the risk factors identified for cIMT and CP differ from those of other ethnicities, suggesting that approaches to risk assessment and early detection should be tailored around the most potent risk factors in this population. The models identified in the current work should be helpful to health systems and policy makers for early detection and effective treatment of subclinical indicators of stroke and ischemic heart disease.

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