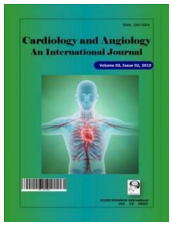

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Sex-related Association of Serum Uric Acid and Carotid Atherosclerosis in a Hypertensive Nigerian Population

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Authors' contributions

This work was carried out in collaboration between both authors. Author NNU designed the study, performed the statistical analysis and wrote the first draft of the manuscript. Authors NNU and MRA managed the analyses of the study and wrote the protocol. Authors NNU and MRA managed the literature searches. Both authors read and approved the final manuscript.

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ABSTRACT

Background: Atherosclerosis is a primary cause of cardiovascular morbidity and mortality. Dyslipidemia is a key risk factor for the development of atherosclerosis. Carotid intima-media thickness (CIMT) is an established tool for the detection and assessment of progression of atherosclerosis. Serum uric acid (SUA) a product of purine metabolism has been recognized as a marker of endothelial dysfunction. The aim of this study was to determine the effect of gender difference in serum uric acid on subclinical carotid atherosclerosis as determined by CIMT in hypertensive patients attending the cardiology clinic of the UPTH.
Methods: 144 Hypertensive subjects and 72 age- and sex- matched controls were recruited. Their waist circumference, body mass indices and fasting lipid profile and SUA were determined. Diabetics and patients receiving uric acid-lowering drugs were excluded. CIMT was measured in all

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study subjects using standard protocol. Results were subjected to linear, multiple, and logistic regression analyses.

Results: Eighty-seven (61.7%) of the cases had hyperuricemia while it was present in 29(39.7%) of the controls (p=0.002). The mean uric acid was significantly higher among the cases when compared to the control group (382.8 ±109.2 µmol/l versus 347.8 ±97.4 µmol/l, p=0.021). The male subjects had a higher SUA levels than the female subjects (415.1± 98.53 µmol/l versus 334.7± 98.50 µmol/l, p<0.001). The mean CIMT of the hypertensive subjects was significantly higher than that of the control cohorts (0.79± 0.19 mm versus 0.62± 0.78 mm, p<0.001). Binary logistic regression analysis of the whole population after adjusting for age, sex, waist circumference, SBP, TG, revealed that the association between SUA and carotid atherosclerosis was significant in men but not in women.

Conclusion: A significantly positive association between SUA level and CIMT was observed in the present sample of hypertensive Nigerian adult population. This association was evident in men with essential hypertension, but not in the women.

Keywords: Serum uric acid; carotid atherosclerosis.

1. BACKGROUND

Hyperuricemia is a metabolic problem that has become quite common over the past several decades. The common clinical issues associated with hyperuricemia are gouty arthritis, gouty tophi, and uric acid kidney stones. For many years, these were the main indications for lowering serum uric acid levels. In recent times however, well-established nonarticular associations between hyperuricemia and chronic kidney disease, coronary artery disease, and hypertension have been described [1]. A number of studies have also shown that serum uric acid (SUA) plays a role in the development of cardiovascular morbidity in patients with hypertension [2,3] type II diabetes [4], and cardiac or vascular diseases [5-7]. Uric acid (UA) is the end product of purine metabolism in humans. Sources of purine are either endogenous, from de novo synthesis or nucleic acid breakdown (approximately 600 mg/day), or exogenous, from dietary purine intake (approximately 100 mg/day) [8]. In the steady state, this daily production and ingestion of approximately 700 mg of UA is balanced by daily elimination of an equal amount of UA from the body.

The mechanism(s) by which SUA may engender organ damage is not fully understood, but there is increasing evidence that this may be mediated via endothelial dysfunction, particularly impaired nitric oxide production, which is a common finding in patients with cardiovascular and renal diseases and is thought to be mediated in part by reactive oxygen species (ROS), dyslipidemia, genetic factors, and other causes [9]. ROS can be generated by several mechanisms, one of which involves reaction of xanthine oxidase with xanthine to generate superoxide anion and uric acid. These ROS cause endothelial dysfunction by reacting with and removing nitric oxide (NO), thereby preventing vasodilation of the endothelium. Decreased NO and increased ROS such as superoxide anion, hydrogen peroxide, hydroxyl radical and peroxynitrite damage the endothelial cells by upregulating the proinflammatory mediators, adhesion molecules and inducing apoptotic cell death contributing to atherosclerosis [10]. There is however a gender difference in UA level; women usually have a lower UA level than men. The association between serum UA and cardiovascular events in the general population is reported to be stronger in women than in men [11]. Other studies have demonstrated that SUA is more closely related with metabolic syndrome in women than in men [12].

Atherosclerosis and its complications are the leading causes of death worldwide. Atherosclerosis seems to progress from childhood. Lipid entrapment, oxidation and their shape-changing in vessel walls lead to a chronic inflammatory state, which in turn transform the former ‘fatty streaks’ into a real fibrous plaque, susceptible to future rupture, thrombosis and stenosis [13]. Clinical manifestations of cardiovascular disease, however, often arise in a stage of well-advanced atherosclerosis; but arterial vessel wall changes occur during a presumably long subclinical lag phase characterized by functional disturbances and by gradual thickening of intima-media [14]. However, a substantial proportion of patients progress abruptly from inapparent disease to a myocardial infarction or possible death, due to

thrombus formation following acute rupture or erosion of non-stenotic plaques [15]. This highlights the importance of detecting atherosclerosis in the early phase of disease to facilitate effective disease modification strategies in predisposed individuals. The measurement of carotid intima-media thickness (CIMT) has emerged as a useful adjunct to risk Stratification since it can identify and quantify the atherosclerotic burden and may lead to interventions that may favorably alter the natural course of cardiovascular disease [16]. Carotid intima-media thickness is a marker of early atherosclerosis, its anatomic extent and progression, and CIMT is increased in subjects with several cardiovascular risk factors and is a predictor of cardiovascular events and end-organ damage [17].

1.1 Aim

Although many studies have been focused on the presence or absence of an independent relationship between uric acid and coronary and cerebrovascular diseases [18,19], thus far no study has examined for the relationship between SUA and carotid atherosclerosis in a Nigerian population. This study was conducted in a Nigerian population to determine if sex differences contribute to the association of SUA, other cardiovascular risk factors and CIMT in subjects with hypertension in a distinctively black African population.

2. METHODS

2.1 Study Population

Study subjects were randomly recruited from newly-diagnosed hypertensive patients attending the general out-patients, and medical out-patients clinics of the University of Port-Harcourt Teaching Hospital from January 2016 to August 2016. Those who were currently taking uric acid-lowering drugs and contraceptive pills were excluded. Cases were also excluded if they had previously been previously diagnosed hypertensive and on anti-hypertensive medication. Diabetics were also excluded from the study. All participants underwent a routine clinical examination, blood biochemical examination and carotid ultrasonography. Finally, 144 newly-diagnosed hypertensive subjects were recruited as cases. Seventy-two apparently healthy age- and sex-matched individuals were randomly selected from hospital staff and patients' relatives and were classified as controls. Written informed consent was obtained from participants and the ethical committee of the hospital.

2.2 Demographic and Clinical Characteristics

Demographic and clinical characteristics such as age and gender were obtained by a structured questionnaire. Blood pressure was measured with a standard mercury sphygmomanometer. Height, weight, waist circumference, hip circumference were measured manually. Body mass index (BMI) was calculated as weight (kilograms) divided by height (meters) squared. Waist-to-hip ratio was also calculated.

2.3 Laboratory Examination

Fasting venous blood were collected and analyzed in the chemical pathology laboratory of the University of Port Harcourt Teaching Hospital for serum uric acid, lipid profile and blood glucose. SUA was analyzed with the colorimetric method using an auto-analyzer. Normal values of SUA are less than 310 µmol/L and less than 410 µmol/L for women and men respectively [20]; therefore individuals with values above these cut-off values were classified as having hyperuricemia. Fasting cholesterol and triglyceride levels were measured using the enzymatic method. Fasting HDL-C was measured with the precipitation method. LDL-C values were calculated using the Friedewald equation when triglyceride level was less than 4.0 mmol/L: LDL-C= TCH- (HDL-C+TG/2.2) [21].

2.4 Carotid Ultrasonography

The study was performed by the same operator who was blinded to the clinical information of the subjects, using Aloka Prosound SSD 4000 echocardiography machine equipped with a 7.5 MHz imaging transducer. Both the left and right carotid arteries were evaluated. The common carotid artery was carefully scanned utilizing standard protocol to identify the thickest CIMT. Intima-media thickness was defined as the distance between the leading edge of the lumen-intima and the leading edge of the media-adventitia. Mean value of the three determinations was calculated and the final values of IMT were averaged by the left and right mean IMT values. A normal CIMT was defined as values between 0.5-1.0 mm [22].

2.5 Statistical Analysis

Data was expressed as mean± standard deviations and frequencies as a percentage. Continuous variables were compared with the Students t-test or one-way analysis of variance as considered appropriate. Proportions or categorical variables were compared with the Chi-square test. Relations among continuous variables were assessed using Pearson correlation coefficient and linear regression analysis. Multiple logistic models were constructed to elucidate the independent determinants of CIMT. The odds ratio and 95% confidence intervals were calculated. All analyses were performed by SPSS statistical software (version 19.0, SPSS Inc). *P* values of <0.05 were considered statistically significant.

3. RESULTS

3.1 Clinical Characteristics

Table 1 summarizes the clinical characteristics and biochemical parameters of the individuals. The age of the study participants with hypertension ranged between 20 and 86 years with a mean age of 51.4±12.9 years. 59.7% of the participants were in the 40-59 years' age-group. The mean age of the control population was 47.9±14.7 years with a range of 24 – 82 years. The case and controls were matched for age (p=0.083).

There were more females than males among the cases in a ratio of 1.32:1 as 56.9% of them were females and 43.1% were males. Among the controls also females accounted for 50.0% giving a female to male ratio of 1:1.

Eighty-seven (61.7%) of the cases had hyperuricemia while it was present in 29(39.7%) of the controls (p=0.002). The mean uric acid was significantly higher among the cases when compared to the control group (382.8 ±109.2 µmol/l versus 347.8 ±97.4 µmol/l, p=0.021) (Table 1). The male subjects had a higher SUA levels than the female subjects (415.1± 98.53 µmol/l versus 334.7± 98.50 µmol/l, p<0.001) (Table 2).

The male hypertensives had a higher prevalence of hyperuricemia than the females (68.3% versus 56.8%) (p=0.163).

On further analysis however, the male subjects had a higher prevalence of hyperuricemia in the earlier age group than their female counterparts; a reversal in prevalence is however noted with advancing age (Table 3). The individuals with hyperuricemia were significantly older than those with normal UA levels (Table 4).

The mean SBP and DBP were comparable between men and women (Table 2). There was however significant differences in the SBP and DBP of the individuals with hyperuricemia and those with normal SUA levels (Table 4). Among the hypertensive population, there was a statistically significant difference in mean systolic and diastolic blood pressures of the individuals with hyperuricemia when compared with those with normal UA levels (Table 5). A similar finding was also noted with the normotensive control group (Table 6).

Table 1. Baseline clinical characteristics of study population

Variables	Cases (n=144) Mean±SD	Controls (n=72) Mean±SD	P value
Age (years)	51.40±12.9	47.9±14.7	0.083
BMI (Kg/m^2)	29.47±4.87	27.17±4.98	0.001
WC (cm)	97.51±11.9	86.11±18.5	<0.001
SBP (mmHg)	149.0±22.5	115.0±11.3	<0.001
DBP (mmHg)	92.95±13.6	70.61±9.12	<0.001
TCH (mmol/L)	5.09±1.19	4.61±0.68	0.002
TG (mmol/L)	1.18±0.48	0.92±0.41	<0.001
HDL-C (mmol/L)	0.89±0.12	1..07±0.51	0.004
LDL-C (mmol/l)	3.50±1.06	3.30±0.66	0.151
SUA (µmol/L)	382.81±109.2	347.8±97.4	0.021
CIMT (mm)	0.79±0.19	0.62±0.77	<0.001

SD= Standard deviation; BMI= Body mass index; WC= Waist circumference; WHR= waist-hip ratio; SBP= Systolic blood pressure; DBP= Diastolic blood pressure; PP= Pulse pressure; TC= Total cholesterol, TG= Triglycerides, HDL-c= High density lipoprotein cholesterol, LDL-c= Low density lipoprotein cholesterol; SUA=Serum uric acid; CIMT= Carotid intima-media thickness

Table 2. Baseline clinical characteristics of study population with respect to gender

Variables	Males Mean±SD	Females Mean±SD	P value
Age (years)	49.00±13.5	51.58±12.3	0.142
BMI (Kg/m^2)	27.0±4.29	30.0±5.14	<0.001
WC (cm)	90.22±16.37	96.53±13.8	0.002
SBP (mmHg)	137.92±24.5	137.18±25.78	0.831
DBP (mmHg)	85.24±16.70	85.54±15.76	0.893
TCH (mmol/L)	4.67±1.03	5.15±1.04	0.001
TG (mmol/L)	1.06±0.41	1.13±0.51	0.346
HDL-C (mmol/L)	0.96±0.38	1.04±0.47	0.171
LDL-C (mmol/l)	3.25±0.89	3.59±0.96	0.010
SUA (µmol/L)	415.10±98.53	334.74±98.56	<0.001
CIMT (mm)	0.74±0.15	0.72±0.20	0.525

SD= Standard deviation; BMI= Body mass index; WC= Waist circumference; WHR= Waist-hip ratio; SBP= Systolic blood pressure; DBP= Diastolic blood pressure; PP= Pulse pressure; TC= Total cholesterol, TG= Triglycerides, HDL-c= High density lipoprotein cholesterol, LDL-c= Low density lipoprotein cholesterol; CIMT= Carotid intima-media thickness

Table 3. Prevalence of hyperuricemia across the different age groups

Age group (years)	Male N (%)	Female N (%)	P value	Total N (%)
20-39	8 (57.1)	6 (42.9)	0.901	14 (100)
40-59	19 (49.3)	36 (50.7)	0.100	55 (100)
60-79	7 (25.9)	20 (74.1)	0.01	27 (100)
≥80	2 (40)	3(60)	0.01	5 (100)

Table 4. Baseline clinical characteristics of study population with respect to SUA level

Variables	Elevated SUA Mean±SD	Normal SUA Mean±SD	P value
Age (years)	52.31±12.27	48.21±13.56	0.021
BMI (Kg/m^2)	29.38±4.99	27.98±4.96	0.041
WC (cm)	95.56±12.88	91.52±17.52	0.054
SBP (mmHg)	143.39±24.66	129.85±22.87	<0.001
DBP (mmHg)	89.57±16.05	80.50±15.11	<0.001
TCH (mmol/L)	4.95±1.07	4.91±1.06	0.801
TG (mmol/L)	1.18±0.44	1.00±0.48	0.006
HDL-C (mmol/L)	0.99±0.44	1.01±0.42	0.837
LDL-C (mmol/l)	3.45±0.93	3.42±0.96	0.792
CIMT (mm)	0.78±0.21	0.68±0.13	<0.001

SD= Standard deviation; BMI= Body mass index; WC= Waist circumference; WHR= Waist-hip ratio; SBP= Systolic blood pressure; DBP= Diastolic blood pressure; PP= Pulse pressure; TC= Total cholesterol, TG= Triglycerides, HDL-c= High density lipoprotein cholesterol, LDL-c= Low density lipoprotein cholesterol; CIMT= Carotid intima-media thickness

The mean waist circumference of the male subjects was 90.22±16.37 cm while that of the women group was 96.53±13.8 cm (p=0.002). Over forty-nine percent of the entire study population was obese with males making up to 19.6% and the females 73.9% (X^2=61.176, p<0.001). The mean BMI of the men was 27.0±4.29 Kg/m^2 while that of the women was 30.0±5.14 Kg/m^2 (p<0.001) (Table 2). We also found that the individuals with hyperuricemia were significantly more obese than those with normal UA levels (p=0.041) (Table 4).

Mean levels of TCH and LDL-C of the men when compared to their female counterparts were (4.67±1.03 mmol/L vs. 5.15±1.04 mmol/L, p=0.001) and (3.25±0.89 mmol/L vs. 3.59±0.96 mmol/L, p=0.010) respectively (Table 2).

Table 5. Clinical and laboratory characteristics of the 144 hypertensive cases with and without elevated SUA

Variable	Elevated SUA Mean ±SD	Normal SUA Mean ±SD	P value
Age (years)	52.14± 12.13	50.15± 14.39	0.380
BMI (kg/m^2)	29.54± 5.08	29.59± 4.53	0.955
WC (cm)	97.68± 10.95	97.54± 12.99	0.945
WHR	0.93± 0.08	0.92± 0.08	0.364
SBP (mmHg)	152.1± 21.8	143.1± 21.1	0.017
DBP (mmHg)	95.17± 14.1	89.12± 12.3	0.020
TC (mmol/l)	5.01± 1.21	5.22± 1.18	0.312
TG (mmol/l)	1.26± 0.47	1.09± 0.47	0.036
HDL (mmol/l)	1.04± 0.50	1.10±0.53	0.478
LDL (mmol/l)	3.44± 1.04	3.61± 1.10	0.389
CIMT (mm)	0.83± 0.21	0.73± 0.15	0.006

SD= Standard deviation; BMI= Body mass index; WC= Waist circumference; WHR= Waist-hip ratio; SBP= Systolic blood pressure; DBP= Diastolic blood pressure; PP= Pulse pressure; TC= Total cholesterol, TG= Triglycerides, HDL-c= High density lipoprotein cholesterol, LDL-c= Low density lipoprotein cholesterol

Table 6. Clinical and laboratory characteristics of the 72 normotensive subjects with and without elevated SUA

Variable	Elevated SUA Mean ±SD	Normal SUA Mean ±SD	P value
Age (years)	44.00± 7.59	40.40± 8.51	<0.001
BMI (kg/m^2)	29.01± 4.80	25.98± 4.84	<0.001
WC (cm)	89.75± 16.07	83.69± 19.76	<0.001
WHR	0.89± 0.06	0.91± 0.21	0.856
SBP (mmHg)	117.1± 9.80	113.5± 12.13	<0.001
DBP (mmHg)	72.50± 7.99	69.16± 9.64	<0.001
TC (mmol/l)	4.77± 0.49	4.51± 0.76	0.001
TG (mmol/l)	0.96± 0.26	0.90± 0.49	0.055
HDL (mmol/l)	0.86± 0.21	0.90±0.18	0.015
LDL (mmol/l)	3.47± 0.51	3.19± 0.73	0.035
CIMT (mm)	0.64± 0.09	0.61± 0.07	<0.001

SD= Standard deviation; BMI= Body mass index; WC= Waist circumference; WHR= Waist-hip ratio; SBP= Systolic blood pressure; DBP= Diastolic blood pressure; TC= Total cholesterol, TG= Triglycerides, HDL-c= High density lipoprotein cholesterol, LDL-c= Low density lipoprotein cholesterol

Twenty (13.9%) of the cases had elevated CIMT while it was not present in the controls (X^2=11.168, p=0.001). The mean CIMT of the hypertensive subjects was significantly higher than that of the control cohorts (0.79± 0.19 mm versus 0.62± 0.78 mm, p<0.001). The mean CIMT of the men was 0.74±0.15 mm while it was 0.72±0.20 mm in the women (p=0.525). 10.3% of the men had elevated CIMT while 8.3% of the women had elevated CIMT (p=0.617). The mean CIMT was significantly higher in the individuals with hyperuricemia when compared to those with normal UA level (p<0.001) (Table 4). In this study, CIMT was significantly higher in hypertensive-hyperuricemic patients (0.83±0.21 mm) than among the hypertensive non-hyperuricemic patients (0.73±0.15 mm, p=0.006) (Table 5). This study also showed that CIMT was higher in normotensive hyperuricemic controls (0.64± 0.09 mm) than among the normotensive non-hyperuricemic controls (0.61± 0.07 mm), and that the difference was statistically significant (p<0.001) (Table 6).

Carotid atherosclerosis (measured by CIMT) significantly correlated with SUA concentration in all patients (r=0.266, p=0.001). When partial correlation analysis was done while controlling for age, SUA concentration was still significantly correlated with carotid atherosclerosis (r=0.102, p=0.024).

In multiple regression analysis, after controlling for age, waist circumference, SBP and TG, SUA was still found to be significantly and independently associated with CIMT in all individuals (Table 7). Multiple regression analysis was done to evaluate the effect of sex on SUA and CIMT relationship, which revealed that the CIMT was significantly and independently associated with SUA concentration in men, but not in women (Table 8). When binary logistic regression analysis of the whole population was performed after adjusting for age, sex, waist circumference, SBP, TG, the association between SUA and carotid atherosclerosis was significant in men but not in women. In this model, the odds ratio (95% CI) of the covariates were as follows: in men, age 1.12 (1.03-1.22), p=0.008; waist circumference 1.05 (0.96-1.14), p=0.254; SBP 1.02 (0.98-1.06), p=0.298; TG 0.142 (0.00-2.34), p=0.172; SUA 1.01 (1.01-1.00), p=0.002, and in women, age 1.19 (1.06-1.33), p=0.003; waist circumference 0.98 (0.91-1.06), p=0.626; SBP 1.07(1.02-1.11), p=0.005; TG 7.37 (1.14-47.52), p=0.036; SUA 0.99 (0.98-1.00), p=0.381.

4. DISCUSSION

The association between hyperuricemia and hypertension and the pathogenesis of atherosclerosis is still unclear. The present study was conducted in order to determine whether there was any relationship between SUA levels and a marker of subclinical target organ damage such as CIMT in non-diabetic essential hypertensive patients and if the relationship was influenced by gender.

In this study, the prevalence of hyperuricemia among the hypertensive case was 61.7% while it was 39.4% among the controls (p=0.002). This was similar to the prevalence rate of 61% reported by Meti et al. [23] in a hospital-based study, but was in contrast to Alikor et al. [24] who reported a prevalence of hyperuricemia of 17.2% in a population-based study in a rural community in the Niger Delta area of Southern Nigeria. Their lower prevalence may be due to the rural-urban dichotomy in the level of SUA which may not be unconnected to the exposure to environmental pollutants [25-27], and the higher prevalence of the components of the metabolic syndrome among the urban population [28,29] which frequently conform with these cardiovascular risk factors.

In this study, the mean SUA values were significantly higher among the hypertensive patients than the control group (p=0.021). This is similar to the result reported by Ofori and Odia in Port Harcourt Southern Nigeria [30] and Lin et al. [31]. This present study also revealed that among the hypertensive cohorts, those with hyperuricemia had significantly higher systolic and diastolic blood pressures than their normo-uricemic counterparts (Table 5). In like manner, among the normotensive cohorts, the individuals with hyperuricemia had significantly higher blood pressures than the normo-uricemic individuals (Table 6).

Table 7. Multiple regression analysis for Carotid Intima-media thickness

Independent variables	β	p-value
Age (years)	0.324	<0.001
WC (cm)	-0.060	0.309
SBP (mmHg)	0.349	<0.001
TG (mmol/L)	0.157	0.007
SUA (µmol/L)	0.162	0.006

Table 8. Multiple regression analysis for Carotid Intima-media thickness in males and females

Independent variables	Males		Females	
	β	p-value	β	p-value
Age (years)	0.304	0.004	0.362	<0.001
WC (cm)	-0.058	0.546	-0.019	0.814
SBP (mmHg)	0.387	<0.001	0.329	<0.001
TG (mmol/L)	0.072	0.408	0.212	0.010
SUA (µmol/L)	0.206	0.024	0.091	0.258

The association between arterial hypertension and hyperuricemia is very common. It has been reported that 25-40% of patients with untreated hypertension and more than 80% with malignant hypertension have hyperuricemia [32]. Hyperuricemia is more common in primary hypertension, especially in patients with hypertension of recent onset and in pre-hypertension associated with microalbuminuria [33]. Several studies using animal models and cell cultures have revealed mechanisms by which UA could cause hypertension. Hypertension develops by UA-mediated renal vasoconstriction resulting from endothelial dysfunction due to reduction in endothelial levels of nitric oxide and activation of the renin-angiotensin system [34,35]. Hypertension also develops by microvascular renal disease caused by the UA over time [36]. The implication is that the normotensive hyperuricemic subjects may potentially develop hypertension in the long run.

In this study, hyperuricemia was observed in 41 (68.3%) of the male hypertensives and 46 (54.2%) of the female hypertensives. This was consistent with Chowdeswari et al. [37] where hyperuricemia was found in 64% of the males and 59% of the females. Although there was a predominance of males with higher UA levels than females in our study, it was not statistically significant. On further analysis however, the male subjects had a higher prevalence of hyperuricemia in the earlier age group than their female counterparts; a reversal in prevalence is however noted with advancing age. We observed that the prevalence of asymptomatic hyperuricemia varied with age between genders. In the male sex, a higher frequency of asymptomatic hyperuricemia was noted in the 20-39 years' age, while it was higher from the sixth-decade onwards for the female. A similar finding was reported by Kuzuya et al. [38]. This study also revealed a mean age of 51.58±12.3 years for the female cohorts. A similar finding was reported by Alikor et al. [24] and Lin et al. [31]. SUA level is known to rise substantially in women after menopause almost approaching the level in men. High levels of endogenous estrogen in premenopausal women or exogenous administration of estrogen in postmenopausal women are thought to promote more efficient renal clearance of urate leading to lower SUA levels [33].

The mean SUA levels in the male subjects were however significantly higher than that of the females (Table 2). This finding was similar to that reported by Lin et al. [31] and Anton et al. [39] because of the uricosuric effect of estrogen.

Interestingly in this study, CIMT was significantly higher in hypertensive-hyperuricemic patients than among the hypertensive non hyperuricemic patients. This means hyperuricemia per se could be a risk factor for atherosclerosis in hypertensive patients and by necessary implication an indicator of increased cardiovascular disease. This is consistent with the findings by Elsayed et al. [40]. This study also showed that CIMT was higher in normotensive hyperuricemic controls than among the normotensive non hyperuricemic controls, and that the difference was statistically significant. This was consistent with the results by Elsayed et al. [40] and Tavil et al. [41]. This means that hyperuricemia could be a risk factor for atherogenesis independent from hypertension. So much so since, increased UA level has been noted to upregulate proinflammatory mediators in vascular smooth muscle cells [42] leading to vascular endothelial dysfunction (VED). VED plays a critical role in pathogenesis of various cardiovascular disorders such as atherosclerosis, hypertension, CAD, and heart failure.

In this study, SUA was positively correlated with CIMT in all hypertensive patients. Furthermore, after controlling for age, TG, WC, and SBP, SUA was still found to be significantly and independently predictive of increased CIMT in men, but not in women. These findings suggest that sex differences played some role in the association of SUA and carotid atherosclerosis in the present study. A similar finding was reported by Kawamoto et al. [43]. Our findings could be explained by hypothesizing that women are protected by estrogen before menopause, either due to the effect of estrogen on renal urate excretion causing a reduction in SUA levels or due to putative anti-oxidant and anti-inflammatory effects of estrogen antagonizing putative pro-oxidant, pro-inflammatory effects of hyperuricemia. Another potential explanation might be that it is the increase in SUA level that occurs in women after menopause that causes the association with increased CIMT, rather than the absolute SUA level. Although men have higher SUA levels that women, their levels remain largely stable in adulthood.

5. CONCLUSION

A significantly positive association between serum UA level and CIMT was observed in the

present sample of hypertensive Nigerian adult population. This association was evident in men with essential hypertension, but not in the women. Sex hormones might account for this association, although the underlying mechanisms were not determined in this study.

6. LIMITATIONS

1. The cross-sectional study design could not determine causal roles of serum UA on development of carotid atherosclerosis.
2. Stratification of the female population into pre-menopausal and post-menopausal may have enabled the investigators to better delineate the putative effect of sex hormones on SUA levels.

CONSENT

As per international standard or university standard, patient's written consent has been collected and preserved by the authors.

ETHICAL APPROVAL

As per international standard or university standard, written approval of Ethics committee has been collected and preserved by the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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