Clinical Medicine Research
2018; 7(1): 1-7
http://www.sciencepublishinggroup.com/j/cmr
doi: 10.11648/j.cmr.20180701.11
ISSN: 2326-9049 (Print); ISSN: 2326-9057 (Online)

Hyperuricemia and Its Correlation with Target Organ Damage and Electrocardiographic Changes in Newly Diagnosed Adult Nigerian Hypertensive Patients

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To cite this article:

Abidemi Jude Fasae, Olusegun Adesola Busari, Rotimi Oluyombo, Musa Yusuf, Oladipo George Opadijo, Ayodele Babatunde Omotoso. Hyperuricemia and Its Correlation with Target Organ Damage and Electrocardiographic Changes in Newly Diagnosed Adult Nigerian Hypertensive Patients. *Clinical Medicine Research.* Vol. 7, No. 1, 2018, pp. 1-7. doi: 10.11648/j.cmr.20180701.11

Received: March 10, 2017; **Accepted**: April 10, 2017; **Published**: January 26, 2018

Abstract: The objective of the study was to determine the prevalence of Hyperuricemia and evaluate its correlation with target organ damage and electrocardiographic changes in newly diagnosed adult Nigerian hypertensive patients. It was a cross sectional study done at the University of Ilorin Teaching Hospital, Ilorin, Nigeria. 150 untreated newly diagnosed hypertensive patients 18 years and above and 115 age and sex-matched normotensive individuals were recruited into the study. Data obtained was analyzed using Epi-Info version 6.04 and Statistical Package for Social Sciences (SPSS) version 14 computer software packages. The prevalence of Hyperuricemia was 36.7% and 17.4% in hypertensive patients and normotensive controls respectively. Mean serum UA in hypertensive patients and normotensive controls was 0.4±0.1mmol/l and 0.3±0.1mmol/l respectively ($p<0.0001$). There was an association between Hyperuricemia and left ventricular hypertrophy ($x^2=23.97$, $p<0.0001$). The study showed that Hyperuricemia is prevalent in adult Nigerians with newly diagnosed hypertension. Hyperuricemia was associated with left ventricular hypertrophy which is common target organ damage and confers an increased risk of cardiovascular events in systemic hypertension.

Keywords: Hyperuricemia, Target Organ Damage, Electrocardiographic Changes, Hypertensive Nigerians

1. Introduction

Systemic hypertension (HT) is a common disease globally, with populations of African descent being most prone to its complications [1-5]. In 2010, HT was the commonest of the three leading risk factors for global disease burden [6]. The reason for the enormous burden of HT has been reported in numerous studies, showing that it is strongly associated with overall cardiovascular risk [6-8]. HT contributes to both cardiovascular and cerebrovascular endpoints, including heart failure (HF), myocardial infarction (MI) and stroke and it accounts for 16.5% of all deaths including 51% of deaths due to strokes and 45% of deaths due to coronary artery disease (CAD) [7, 8]. The prevalence of HT has been increasing globally and it has been estimated that it will increase to 29.2% by 2025 [2]. In Nigeria, studies have reported prevalence varying from 12% to 36.6% [9-13]. HT is implicated in 35% of all atherosclerotic cardiovascular events, including over 40% of all cases of HF [14-17]. In the US, 33.0% of adults aged 20 years and older have HT. African American adults have among the highest prevalence of HT (44%) in the world [18]. The Framingham and other epidemiological surveys as well as experimental studies have shown that hyperuricemia (HU) significantly increases the risk for cardiovascular disease

and complications [17, 19, 20].

Some studies done in Nigeria and other developing countries have shown that the prevalence of HU can be high in hypertensive patients in developing countries, thereby underscoring its importance as a cardiovascular risk factor [21, 22]. There are a few reports about HU in untreated hypertensive adult Nigerians [21, 23]. Abengowe [23] investigated the relationship between HU, untreated HT and alcohol consumption in Nigerian men and excluded women. Also, Adedeji and Onitiri [22] studied HU and serum lipid abnormalities in Nigerian hypertensive patients but included those who were on antihypertensive drugs.

The objective of the study was to determine the prevalence of HU and evaluate its correlation with target organ damage (TOD) and electrocardiographic (ECG) changes in newly diagnosed adult Nigerian hypertensive patients.

2. Materials and Methods

2.1. Study Design and Study Site

The study was a cross sectional study done at the General Out-patient Department (GOPD), Medical Out-patient Department (MOPD) and Emergency Room (ER) of the University of Ilorin Teaching Hospital, Ilorin, in the North Central geopolitical zone of Nigeria between May 2007 and October 2007.

2.2. Ethical Considerations

The study protocol was approved by the Ethics and Research Committee of the hospital, and both oral and written consent was obtained from all the participants.

2.3. Study Participants

One hundred and fifty (150) untreated newly diagnosed hypertensive patients 18 years and above and one hundred and fifteen (115) age and sex-matched normotensive individuals were recruited into the study. Excluded from the study were participants with significant history of alcohol ingestion; those on drugs such as lipid lowering drugs, uricosuric agents, antituberculous and antiretroviral drugs; cancer patients taking or not taking cytotoxic drugs; patients with renal impairment and diabetes mellitus (DM).

2.4. Clinical Evaluation, Measurements and Definitions

All participants had a detailed history and a thorough physical examination, including anthropometry.

2.4.1. Anthropometry

Each participant's height in meters was determined using Marsden's Stadiometer with maximum height of 2 meters. The measurement was performed to the nearest 0.1 cm. Weight in kilogram was determined using Detecto electrical column scale; model CN 20 with 180 kg capacity. The body weight was measured to the nearest 0.1kg and the body mass index (BMI) (Kg/m^2) [24] was determined by dividing the weight (Kg) by the square of the height (m). The waist circumference (WC) (cm) was measured with a tape at the umbilical level on the bare abdomen, and the hip circumference (HC) (cm) measured at the external margins of the anterior superior iliac spines and waist/hip (WHR) ratio was determined [25]. Abdominal/central obesity was defined as WHR: > 1.0 (men), > 0.9 (women), WC: > 102 cm (40 in) > 88 cm (35 in) in women. Overweight and obesity were also defined as: BMI ≥ 25 kg/m^2 and ≥ 30 kg/m^2 respectively.

2.4.2. Blood Pressure Measurement

Blood pressure was measured using mercury column sphygmomanometer (Accosson) and a cuff of appropriate size (25 cm x 12 cm). A standardized protocol was followed, in which systolic (SBP) and diastolic blood pressure (DBP) was measured on the right arm after at least 5 min of rest. Two consecutive measurements were obtained 5 minutes apart and the average was obtained. Phase I Korotkoff sound was used for SBP and phase V for the DBP. HT was defined as SBP ≥140 mmHg and/or DBP ≥90 mmHg, or use of antihypertensive drugs [26-29].

2.4.3. Precordial and Arterial Wall Examination

The precordium was examined for the location and character of the cardiacapex, presence of a fourth heart sound (S4), and intensity of the aortic component of the second heart sound (A2). The radial pulse was examined for arterial wall thickening (cord-like artery on palpation) [30].

2.4.4. Funduscopy

Each participant had funduscopic examination done by the principal investigator using Keeler® ophthalmoscope. The retina was examined for arteriovenous nicking, copper/silver wiring of the retina vessels, cotton wool exudates / flame-shaped hemorrhages and papilledema. Hypertensive retinopathy was graded according to the Keith-Wagener-Barker classification [31] into:

Grade 1: Copper/Silver wiring of retinal arteries

Grade 2: Grade 1 plus arteriovenous nicking

Grade 3: Grade 2 plus cotton wool exudates / flame-shaped hemorrhages

Grade 4: Grade 3 plus papilledema

2.4.5. Electrocardiography

All participants had a 12-lead resting electrocardiogram (ECG) done in supine position using Schiller Cardiovit AT-2 machine at 25mm/s speed and sensitivity of 10mm/mV in the hospital, and was interpreted by the principal investigator and subsequently vetted by a cardiologist. The ECG tracings were examined for left atrial enlargement (LAE), left ventricular hypertrophy (LVH) with or without strain pattern / ischemia, infarction, heart blocks, arrhythmias and resultant QRS axis. LAE and LVH were determined using Araoye criteria [32, 33] which state thus:

1. LAE= P terminal force in lead V_1>1mm or P wave notching >40msec or a "*Macruz"* index [34] >3.
2. LVH= (1) $SV_2 + RV_6$>4.0mV (Male); >3.5mV (Female)
3. Flat or inverted T wave ("*Strain pattern*") in V_5 or V_6
4. R_1 amplitude > 1.2mV

2.4.6. Serum Uric Acid Measurement

Serum uric acid level was estimated at the Chemical Pathology laboratory of the hospital using Fe (III) reduction direct method with Intraseries and Interseries Variation Coefficient of 2.09% and 2.38% respectively and Recovery of 96.6%. Hyperuricemia was defined as serum UA level > 0.42m mol/L for males and > 0.36m mol/L for females.

2.4.7. Other Laboratory Measurements

Venous blood samples were collected from the study participants for fasting serum lipids assay, serum electrolytes panel and serum urea (BUN) and creatinine, fasting blood glucose (FBG) and others.

2.5. Data Analysis

Data obtained was analyzed using Epi-Info version 6.04 and Statistical Package for Social Sciences (SPSS) version 14 computer software packages. Results for continuous variables were expressed as mean±SD and proportions as percentages. The Chi square (x^2), with Yate's correction where applicable, was used to determine the statistical significance of categorical variables between the different groups. Student's t-test was used to assess the significance between means of two groups. Pearson's correlation coefficient was used to assess the correlation between measured variables. Cross-tabulation was performed to investigate the associations of different variables with serum uric acid. P value $\leq$ 0.05 was considered statistically significant.

3. Results

Fifty two (34.7%) of the 150 newly diagnosed hypertensive patients were males while 98 (65.3%) were females, with age range of 19-85 years and a mean age of 50.4±12.3 years. The mean age and range of the normotensive controls are shown in Table 1. No statistical difference was observed in the mean ages of the patients and the controls (p = 0.67). Table 1 shows the other sociodemographic characteristics of the patients and controls. Mean SBP and DBP of the hypertensive patients are 175±24.0mmHg and 106±16.4mmHg respectively; and 119.8±9.1mmHg and 78.2±8.3mmHg respectively for normotensive controls (SBP, p<0.0001; DBP, P<0.001). Other clinical characteristics of the hypertensive patients and the normotensive controls are presented in Table 2.

The prevalence of HU was 36.7% and 17.4% in hypertensive patients and normotensive controls respectively. Mean serum UA in hypertensive patients and normotensive controls was 0.4±0.1mmol/l and 0.3±0.1mmol/l respectively (p<0.0001). In the hypertensive patients, males had higher mean serum UA than females (0.4±0.1mmol/l vs 0.3±0.1mmol/l, p=0.01). The mean serum TC in hypertensive patients was 5.1±1.1mmol/l and in normotensive controls 3.6±1.5mmol/l (p<0.001). Table 3 shows the other biochemical characteristics of the patients and the controls. One hundred and twenty nine (86.1%) of hypertensive patients had abnormal ECG compared to 18(16.5%) in the normotensive controls (p<0.0001). Among the hypertensive patients; 28.7% had LVH alone, 21.3% had LAE alone, and 27.3% had both LVH and LAE. Other ECG findings are presented in Table 4.

There was an association between HU and LVH (x^2=23.97, p<0.0001). Table 5 presents the mean serum UA in various ECG characteristics. As shown in Table 6, mean serum UA was higher in hypertensive patients with LVH than those with normal ECG, however, not statistically significant (0.4±0.1mmol/l vs 0.3±0.1mmol/l, p=0.2). Seventeen percent of hypertensive patients had HU (mean serum UA=0.5±0.1mmol/l) with LVH while 40% of hypertensive patients had LVH with normal serum UA (mean serum UA=0.3±0.1mmol/l) p<0.001 (Table 6).

4. Discussion

In this study, more females than males were examined in both hypertensive patients and normotensive controls with male: female ratio of 1:1.9 (p<0.0001) and 1:1.4 (p=0.02) respectively. This might be due to the fact that females tend to seek medical attention earlier and more frequently than males. The prevalence of HU in hypertensive patients was 36.7%. This is lower than the 55% and 52.9% reported by Obeka (21) and Murugan *et al* [35] respectively, and higher than figures (26%-33%) reported in studies on Caucasians [36, 37]. The potential mechanisms behind the link between HU and HT, cardiovascular and renal abnormalities include nitric oxide and renin-angiotensin-aldosterone system (RAAS) pathways [38, 39]. HU may cause endothelial cell dysfunction via nitric oxide synthetase [40-42] and stimulate proliferation of vascular smooth muscle cell [43, 44]. It may also directly stimulate the renin-angiotensin-aldosterone system [45, 46]. Uric acid may also cause renal afferent arteriolopathy and tubulointerstitial disease, leading to chronic kidney disease and HT [47].

There was a significant association between serum UA and LVH (p<0.001), presence of accentuated A2 (p<0.001), S4 (p=0.025) and displaced apex beat (p=0.005). It was observed that the mean serum UA was higher, though not significant, in hypertensive patients with these signs of target organ damage (TOD) than in those without these signs. These findings corroborate those reported by Viazzi *et al* [48] that the association between serum UA and early hypertensive damage suggests that mild HU might be a marker of incipient cardiovascular involvement and may be associated with increased morbidity in hypertensive patients. Also, in this study, the association between serum UA and LVH was stronger in males (p=0.02) than in females (p=0.04). This is in contrast to what was found by Viazzi *et al* [48]. This might be due to higher serum UA and greater left ventricular mass in males than in females [49], especially people of African descent [50].

Target organ damage (LVH and accentuated A2) was found more frequently in hypertensive patients with higher levels of serum TC and LDL-c than their counterparts with

normal levels. This finding is in consonance with that reported by Giuseppe *et al* [51] and Mule *et al* [52]. The association of these metabolic parameters with cardiac hypertrophy (LVH) might be explained by insulin resistance and the accompanying hyperinsulinemia, which are regarded as the pathophysiological key features underlying metabolic syndrome [53, 54]. Trophic effect of insulin on myocardial tissue has been demonstrated in cell cultures and animal models [55], and may be mediated, at least in part by the insulin-like growth factor [56]. In addition, insulin may affect left ventricular mass indirectly by increasing sodium retention or endothelin-1 level, or by inducing sympathetic activation [57].

5. Conclusion

The study reveals that HU is prevalent in adult Nigerians with newly diagnosed HT. HU was associated with LVH which is common target organ damage and confers an increased risk of cardiovascular events in HT. Thus, the study recommends a routine baseline evaluation of serum UA in newly diagnosed hypertensive patients and periodic assessment in patients on antihypertensive drugs.

Table 1. *Sociodemographic characteristics of hypertensive patients and normotensive controls.*

	Hypertensive patients	**Normotensive controls**	**X^2**	**P**
Age				
Mean	50.4±12.3	50.7±12.7		
Range	19-85	23-80		
Sex				
Male	52(34.7)	49(42.6)		
Female	98(65.3)	66(57.4)		
Marital Status				
Single	12(8)	17(14.8)	3.07	0.3
Married	78(52)	63(54.8)	0.2	0.004
Widowed	40(26.7)	22(19.1)	2.06	<0.001
Divorced	20(13.3)	13(11.3)	0.25	<0.001
Education				
Nil	34(22.6)	25(21.7)	0.03	0.86
Primary	46(30.7)	21(18.3)	5.30	0.02
Secondary	41(27.3)	13(11.3)	10.31	0.001
Postsecondary	29(19.4)	56(48.7)	25.76	<0.001

Table 2. *Clinical characteristics of hypertensive patients and normotensive controls.*

Normotensive controls	**Hypertensives patients**	**Variables**	**Normo Hypert**	**Males Females**	**Males Females**	
	(n=115)	**(n=150) p value**	**(n=49)**	**(n=66) p value**	**(n=52)**	**(n=98) p value**
Age (yrs)	50.7(12.7)	50.4(12.3) 0.8	50.8(15.8)	51.4(16.3) 0.81	51.0(12.7)	50.1(12.1) 0.67
BMI (Kg/m^2)	23.3(4.2)	27.2(15.8)<0.0001*	23.2(4.1)	23.4(4.4) 0.76	25.6(5.5)	27.9(5.7) 0.02*
SBP (mmHg)	119.8(9.0)	175.2(24.0) <0.0001*	118.4(9.9)	120.6(9.8) 0.24	177.2(26.9)	174.1(22.4) 0.45
DBP (mmHg)	78.3(8.3)	106.0(16.4) <0.0001*	77.8(9.4)	77.6(7.5) 0.90	108.8(16.8)	104.5(16.1)0.13
WC (cm)	83.1(12.3)	93.4(12.9) <0.0001*	83.0(12.0)	83.2(12.7) 0.93	92.3(14.9)	94.2(11.6) 0.37
WHR	0.96(0.1)	0.98(0.1) 0.06	0.97(0.1)	0.94(0.1) 0.002*	1.01(0.1)	0.96(0.1) 0.0001*
Art wall	2.6%	69.3% <0.0001*	16.3%	9.1% 0.24	76.9%	65.3% 0.14
LMB	1.7%	53.3% <0.0001*	14.3%	3.0% 0.06	73.1%	42.9% 0.0004*
A2	4.3%	66.0% <0.0001*	14.3%	7.6% 0.24	63.5%	67.3% 0.63
S4	1.7%	25.3% <0.0001*	2.0%	1.5%	19.2%	28.6% 0.21
Fundi+	4.4%	38.0% <0.0001*	6.1%	3.0% 0.73	51.9%	29.6% 0.007*
Abloc	0.9%	15.3% 0.0001*	1.5%	--	25.0%	10.2% 0.02*
Abch	1.7%	28.7% <0.0001*	3.0%	--	23.1%	31.6% 0.27

Data are presented as mean (SD);*Differences are statistically significant; Art wall = Arterial wall –thickened;
LMB = Locomotor brachialis – present; A2 = Aortic component of the second heart sound - loud;
S4 = Fourth heart sound - present; Abloc = Apex beat location – displaced; Abch = Apex beat character – Heaving;
+≥ Grade 2 hypertensive retinopathy; BMI – body mass index; SBP – Systolic blood pressure; DBP – diastolic blood pressure;
WC – waist circumference; WHR – Waist – hip ratio. Norm – Normotensives, Hypert - hypertensives

Table 3. *Biochemical characteristics of hypertensive patients and normotensive controls.*

Normotensive controls	**Hypertensives patients**	**Variables**	**Normo Hypert**	**Males Females**	**Males Females**	
	(n=115)	**(n=150) p value**	**(n=49)**	**(n=66) p value**	**(n=52)**	**(n=98) p value**
UA (mmol/l)	0.3(0.1)	0.4(0.1) <0.0001*	0.3(0.2)	0.3(0.1) 0.004*	0.4(0.1)	0.3(0.1) 0.01*
FBG (mmol/l)	4.5(1.2)	4.2(0.9) 0.13	4.7(1.0)	4.4(1.4) 0.29	4.4(0.7)	4.2(0.9) 0.39
TC(mmol/l)	3.6(1.5)	5.1(1.1) <0.0001*	3.6(1.4)	3.6(1.6) 0.88	5.1(1.0)	5.1(1.2) 0.92
LDL-c(mmol/l)	2.2(1.0)	3.1(1.1) <0.0001*	2.2(0.9)	2.2(1.0) 0.90	3.1(1.1)	3.2(1.2)0.71
HDL-c (mmol/l)	1.4(0.4)	1.5 (0.6) 0.88	1.4(0.4)	1.5(0.4) 0.09	1.4(0.5)	1.5(0.6) 0.88
TG(mmol/l)	1.1(0.5)	1.2(0.5) 0.10	1.4(0.8)	1.4(0.9) 0.68	1.3(0.6)	1.2(0.5) 0.56

Normotensive controls	Hypertensives patients	Variables	Normo Hypert	Males Females	Males Females	
	(n=115)	(n=150) p value	(n=49)	(n=66) p value	(n=52)	(n=98) p value
TC/HDC-c	1.9(1.1)	2.7(2.2) 0.002*	1.8(1.2)	1.6(0.9) 0.24	2.4(1.4)	2.8(2.5) 0.36
BUN(mmol/l)	3.7(1.5)	5.3(1.7) <0.0001*	3.9(1.5)	3.7(1.6) 0.45	5.3(1.7)	4.8(1.0) 0.16
Cr(µmol/l)	94.2(19.0)	95.4(15.3) 0.75	96.8(13.8)	92.8(21.9)0.36	94.7(15.3)	90.3(22.7) 0.31

Table 4. *Electrocardiographic characteristics of hypertensive patients and normotensive controls.*

	Hypertensive patients	Normotensive controls	p value
	(n=150)	(n=115)	
Normal ECG	28(18.7)	99(86.1)	<0.0001
LAE alone	40(21.3)	7(6.1)	<0.0001
LVH alone	43(28.7)	3(2.6)	<0.0001
LAE + LVH	41(27.3)	6(5.2)	<0.0001
Heart blocks	4(2.7)	-	
Atrial fibrillation	1(1.3)	-	
Other arrhythmias	-	-	

Table 5. *Mean serum uric acid and electrocardiographic characteristics in hypertensive patients.*

Variables	Mean SUA
Normal ECG	0.30(0.1)
LVH	0.4(0.1)
LAE	0.3(0.1)
Heart blocks	0.3(0.1)
*Arrhythmia	0.4(0.1)

Values are expressed as Mean (SD). *Only two patients had arrhythmia (Atrial fibrillation)

Table 6. *Comparison of means serum uric acid in left ventricular hypertrophy, normal electrocardiogram and other electrocardiographic abnormalities.*

	N	Mean (SD)	t	p value
LVH	83	0.4(0.1)		
Other ECG abnormalities	38	0.3(0.1)	1.2	0.32
LVH	83	0.4(0.1)		
Normal ECG	29	0.3(0.1)	0.6	0.20

Table 7. *Mean serum uric acid in hypertensive target organ damage.*

Variables	N	Mean serum UA	t	p value
Loud A2	99	0.4(0.1)		
Normal A2	51	0.4(0.1)	-0.19	0.84
Present S4	38	0.3(0.1)		
Absent S4	112	0.4(0.1)	0.49	0.63
Hyper Retin.	57	0.4(0.1)		
Normal Fund.	93	0.4(0.1)	-0.04	0.97
Displaced AB	23	0.4(0.1)		
Normal AB	127	0.4(0.1)	-0.38	0.71
Heaving AB	107	0.3(0.1)	0.74	0.60

p<0.05; Hyper Retin=Hypertensive Retinopathy; AB=Apex Beat; Fund=Fundus

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