Original Article

Variation of Serum Uric Acid with Renal Function, Fasting Blood Glucose and Blood Pressure in Northern Cameroonians with Essential Hypertension

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Abstract

Aim/Background: Hyperuricemia has been purported to be associated with renal and cardiovascular events as well metabolic syndrome. We aimed at investigating the relationship between serum uric acid levels and renal function markers in hypertensive patients. **Methods:** Individuals diagnosed with hypertension were consecutively recruited into this cross-sectional study over a period of four months commencing February 2015. Fasting whole blood samples and blood pressure measurements were collected, and data were analysed using the SPSS version 20.0 (IBM corporation, USA) software with statistical significance considered at P<0.05. **Results:** Among 100 participants, 20% had raised serum uric acid levels. While uric acid levels correlated with serum creatinine (r=0.37; P<0.001) and urea(r=0.31; P<0.01), and inversely varied with glomerular filtration rate(r= -0.24; P=0.02), no significant associations were observed between uric acid levels and blood pressure. Furthermore, the mean creatinine level was significantly higher in male participants with elevated uric acid levels compared to those with normal levels [1.67(0.74) mg/dl versus 1.44(0.80) mg/dl; P<0.001). Although male hypertensive participants demonstrated significantly higher mean uric acid level compared to females [7.37(2.51) vs. 6.21(1.57); P<0.01], the prevalence of raised SUA levels was significantly higher women compared to men (50.8% vs. 28.2%; P<0.001). **Conclusion:** Serum uric acid level is associated with kidney function capacity in hypertensive persons, especially in the male gender, and may represent an accessory treatment target in retarding the progression of renal complications.

Keywords: Uric Acid; Blood glucose; Renal Function; Essential Hypertension

Introduction

Uric acid is a waste product of endogenous purine and ATP metabolism in humans, which is exclusively excreted by the kidneys in a less soluble form owing to the absence of the enzyme uricase in humans. [1,2] which catalysis uric acid breakdown rendering it more soluble and easy to excrete. [3] Plasma uric acid levels therefore depend almost entirely on renal excretory capacity as a function of the rate of uric acid production and dietary intake as well as excess alcohol consumption and pathologies involving increase cell turnover such as in leukemias, lymphomas, solid tumors and a variety of cell lysis processes. [4]

Since the inception of the phenomenon of the involvement of elevated plasma uric acid levels in the occurrence of gout in the 1800s, [5] several studies have suggested hyperuricemia as a possible independent and modifiable risk factor in the occurrence and progression of gout, [6,7] obesity, [8] type 2 diabetes, [9,10] metabolic syndrome, [11-13] cardiovascular, [14] and renal events, [15-17] while others portray it to be a treatment target in cardiovascular and kidney disease states. [18-20] Furthermore, various authors have reported hyperuricemia to at best precede hypertension and chronic kidney disease (CKD) or at least occur more frequently among persons with these diseases. [21,22]

Several animal studies have demonstrated that increasing plasma uric acid independently increases the risk of hypertension, chronic kidney disease, and the progression of renal and cardiovascular events. Moreover, as proposed by many animal and human studies, hyperuricemia results in a depreciation of cardiovascular and renal function by lowering endothelial nitric oxide levels and reducing neuronal nitric oxide synthase in the macula densa of the kidney thus are stimulating the renin-angiotensin system. Also it may induce an inflammatory reaction, probable glomerular damage, tubular ischaemia, endothelial dysfunction, and the development of renal microvascular disease owing to the stimulation of vascular smooth muscle cell proliferation thus the installation of renal and systemic hypertension. [2,23-26] Although not yet globally acknowledged as an independent cardiovascular and renal disease risk factor,

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[27-32] hyperuricaemia indeed occupies a vital position owing to its supposed involvement in the initiation and worsening of cardiovascular and renal function, making it an indispensable factor in the management of patients with hypertension and CKD in view of slowing down disease progression and curbing cardiovascular and renal morbidity and mortality. We set out thus to investigate the relationship between serum uric acid levels, blood pressure, and kidney function parameters among hypertensive patients in north Cameroon.

Patients and Methods

Study design and sample collection

Participants were progressively enrolled during the first 4 months of this descriptive cross-sectional study carried out at the General Medicine Services of the Ngaoundere Regional and Protestant Hospitals, commencing from February 2015 and spanning a total period of 6 months. Hypertension was defined as blood pressure (BP) >140/90mmHg and participants were excluded for pregnancy, diabetes, HIV/AIDS, dyslipidemias, cancer and refusal to consent to the study. Subsequently, they were furnished with extensive information on the usefulness and inconveniences of the study, and a written consent to participate obtained. A structural questionnaire was used to collect information on socio-demography, medical and family history, with communication principally in the French, English and local languages. BP and weight measurements were performed and 5ml of fasting whole blood was collected and immediately analyzed for fasting whole blood sugar (FBS) and the rest left to clot in dry tubes on bench-top. The clotted blood samples were centrifuged at 2000rpm for 3 minutes with the resulting serum decanted into Eppendorf tubes and stored at -20°C prior to weekly badge analyses for uric acid, creatinine and urea levels. Glomerular filtration rate (GFR) was estimated using the Modification of Diet in Renal Disease (MDRD) and Cockcroft-Gault (CG) formulas. All procedures were performed following standard operating procedures.

Clinical and biochemical measurements

Blood pressure

An electronic blood pressure machine (OMRON-HEM-712CN2, Serial number: 64167999LF, USA) was used to measure resting BP. Patients were required to rest for at least 15 minutes upon arrival and BP measurements were obtained from both the right and left arms per patient within an average time lapse of 2-3 minutes, and the mean systolic and diastolic pressures between both arms calculated and recorded.

Biochemical parameters

Blood sugar measurements were carried out on fasting whole blood samples using a glucometer (EasyTouch ET-101 Serial number: 1012A002911, Bioptik Technology Inc, Taiwan) having reference range as 75–115 mg/dl. Serum uric acid (SUA), creatinine and urea levels were measured using a Semi-Auto Chemistry Analyser (Mindray BA-88, Serial number: BH7AB2710, China) based on enzyme colorimetry (Uricase-TBHBA), Jaffe and Berthelot methods respectively, with normal values stated at 3.5–7.2 mg/dl, 0.7–1.4 mg/dl and 18–55 mg/dl for males and 2.5–6.0 mg/dl, 0.5–1.1 mg/dl, and 15–43 for females respectively. GFR was estimated using both the Modification of Diet in Renal Disease [33] and the Cockcroft-Gault [34] formulas.

Quality assurance

All pre-analytic processes made use of appropriate glass and plastic ware, specimen transport and storage procedures. Method calibration was ensured by the use of a Calimat multiparameter calibrator (Reference: 62321, Lot: 1003001280, Biomérieux, France). The quality of biochemical analyses was verified and results validated using a LYOTROLTMN control serum (Reference: 62373, Lot: 1003001280, Biomérieux, France). Measurements of biochemical parameters for the first 10 participants were replicated using a second semi-automated spectrophotometer (SECOMAM Basic/70V B0358, SN: 1790) to check for reproducibility of results and evaluate analytical performance. Likewise, automated BP measurements were compared with those obtained using a manual sphygmomanometer.

Ethical considerations

This study obtained ethical clearance from the Ngaoundere Regional Hospital Ethical Committee (Ref: 1227/L/RC/RA/DSP/HR/NGD/CLE). Individuals were reserved the right to freely participate and terminate participation without any sanctions. Participant's information was strictly confidential and referrals to a nephrologist were done by the investigating cardiologist in cases of abnormal results.

Data management and analysis

Microsoft Excel spreadsheets were used to record and clean data prior to analysis with the statistical package for social sciences (SPSS) version 20.0 (IBM corporation, USA). Primarily, sub-data sets were tested for normality using the Kolmogorov-Smirnova and Shapiro-Wilk tests of normality. Correlations between parameters were investigated using the Pearson and Spearman correlation coefficients while the equality of means was tested using the ANOVA and Mann-Whitney U tests. Statistical significance was stated at $P<0.05$.

Results

100 participants matched our inclusion criteria among which were 31 men and 69 women, ranging in age from 17 to 93 years old and having a mean age of 56.1(15.5) years. The mean systolic BP, diastolic BP, SUA, creatinine and urea levels were 163.7(30.1) mmHg, 96.8(19.9) mmHg, 6.7(2.1) mg/dl, 1.6(2.1) mg/dl, 53.8(39.9) mg/dl respectively. Raised uric acid levels were observed in 20% (20/100) of the study participants.

SUA levels demonstrated a direct relationship with serum creatinine and urea measurements, and further correlated negatively with estimated GFR (C-G) in the general study population, but recorded no significant relationship with both systolic and diastolic BP [Table 1].

In addition to the aforementioned relationships observed in the general study population (with the exception of the SUA-Urea relationship), gender-based analyses revealed a significant positive relationship between SUA levels and FBS in male participants but not in their female counterparts [Table 1].

Table 1: Correlation between SUA and selected clinical and biochemical parameters in the general study population, male and female participants.

Category	Parameters		SBP	DBP	FBS	Creatinine	Urea	GFR-CG	GFR-MDRD
All Participants	UA7	r	-0.055	-0.023	0.183	0.366*	0.311*	-0.240*	-0.183
		p-value	0.590	0.819	0.068	<0.001	0.002	0.016	0.069
Male Participants	UA7	r	-0.096	0.052	0.381*	0.386*	0.312	-0.325*	-0.295
		p-value	0.559	0.754	0.017	0.015	0.053	0.044	0.069
Female Participants	UA7	r	-0.034	-0.038	-0.024	0.236	0.199	-0.204	-0.056
		p-value	0.793	0.772	0.852	0.067	0.125	0.114	0.669

*P<0.05

We went on to compare the means of selected parameters between "normouricemic" and "hyperuricemic" participants between who no significant differences were recorded in the general study population. It was observed that the mean serum creatinine was significantly higher in "hyperuricemic" compared to "normouricemic" male participants (but not in females). Both systolic and diastolic BP failed to demonstrate statistical differences between "normouricemic" and "hyperuricemic" participants [Tables 2 and 3].

Table 2: Comparison of means of selected parameters between "normouricaemic" and "hyperuricaemic" in male participants.

Parameters	SUA level	*n*	Mean ± SD	P-value
Age (years)	Normal	28	58.50 ± 16.59	0.374
	High	11	63.45 ± 11.94	
Weight (Kg)	Normal	28	67.43 ± 14.66	0.524
	High	11	70.91 ± 16.60	
SBP (mmHg)	Normal	28	162.71 ± 25.36	0.374
	High	11	171.82 ± 35.44	
DBP (mmHg)	Normal	28	91.61 ± 18.65	0.062
	High	11	103.64 ± 14.33	
FBS (mg/dl)	Normal	28	108.89 ± 32.01	0.109
	High	11	129.73 ± 46.94	
Creatinine (mg/dl)	Normal	28	1.44 ± 0.80	0.031*
	High	11	1.67 ± 0.74	
Urea (mg/dl)	Normal	28	57.32 ± 34.38	0.261
	High	11	64.82 ± 35.05	

*P<0.05

Table 3: Comparison of means of selected parameters between "normouricemic" and "hyperuricemic" in female participants.

Parameters	UA[1] level	*n*	Mean±SD	P-value
Age (years)	Normal	30	53.20 ± 13.86	0.839
	High	31	54.00 ± 16.62	
Weight (Kg)	Normal	30	67.03 ± 18.30	0.885
	High	31	65.03 ± 15.55	
SBP (mmHg)	Normal	30	168.13 ± 33.73	0.184
	High	31	157.39 ± 28.52	
DBP (mmHg)	Normal	30	100.83 ± 22.94	0.158
	High	31	95.13 ± 18.71	
FBS (mg/dl)	Normal	30	97.97 ± 19.85	0.933
	High	31	98.42 ± 22.22	
Creatinine (mg/dl)	Normal	30	1.59 ± 0.80	0.174
	High	31	1.61 ± 0.74	
Urea (mg/dl)	Normal	30	42.37 ± 33.66	0.189
	High	31	49.83 ± 50.20	

*P<0.05

Comparing the mean SUA level between gender, male compared to female participants recorded significant higher levels [7.4(2.5) vs. 6.2(1.6); P<0.01), although a greater proportion of women had raised SUA levels compared to men [50.8% (31/61) vs. 28.2% (11/39); P<0.001].

Discussion

Hyperuricemia has previously been reported by several authors to be associated with both renal impairment [23,35] and cardiovascular events. [36-38] In this study carried out on 100 hypertensive persons, the prevalence of raised SUA was estimated at 20%, results which differ from the increased rates of 46.1% reported by Ofori and Odia among newly diagnosed, untreated hypertensive Nigerians. [39] In an earlier study, hyperuricaemia was estimated in 25% of hypertensive patients without treatment, 50% of patients on diuretic therapy, and in more than 75% of patients with malignant hypertension. [40] A recent study reported a 30.6% hyperuricaemia rate in patients with essential hypertension compared to 10.6% in healthy controls. [41] These disparities may be a direct consequence of the quality of our participants, being a composition of both newly diagnosed and known hypertensive patients, 91(91%) of whom were on antihypertensive pharmacotherapy with varying durations of treatment.

This study demonstrates an increase in SUA levels with increasing serum urea, creatinine, and decreasing GFR among hypertensive participants in general and further with increasing blood glucose levels in males. In line with reports of previous authors, this may be a result of a progressing glomerular damage, endothelial dysfunction, renal microvascular disease and tubular ischaemia [38,42-45] and the predictive nature of hyperuricaemia to diabetes. [9,10] Paradoxically a previous animal study by Kosugi and co-workers hold that diabetes could be a predisposing factor to hyperuricaemia as they observed that diabetic rats were more likely to develop hyperuricaemia compared to the non-diabetic. [46] Elevated uric acid levels have been purported to predict progression of CKD, [47-49] and as GFR falls, SUA levels increase, with about 50% of such patients becoming hyperuricemic prior to the commencement of dialysis. [50] Furthermore, the mean SUA level was significantly higher in males than in females (P=0.005), supporting previous findings, [42-45] probably being a result of the increased vulnerability of males to hyperuricaemia than females, although Luk and Simkin earlier reported that with increasing age such differences tend to dampen. [51] Conversely, Ofori and Odia observed higher mean SUA levels in female hypertensives compared to their male counterparts. We also noted that the proportion of female participants with raised SUA levels was significantly higher compared to the male participants (50.8% vs. 28.2%; P<0.001). Emokpae et al. reported 62% and 59% raised SUA in females and males respectively, which was purported to be associated with the complex interplay of sex hormones in women. [44]

Limitations

This study was a cross sectional survey to examine the association between serum uric acid, arterial blood pressure and renal function markers, and thus did not permit the establishment

of a cause and effect relationship. Hindering enough was the fact that over 60% of our study participants were on at least a single antihypertensive medication and with the absence of a control population, it was difficult to rule out the concomitant effect of antihypertensive pharmacotherapy on arterial blood pressure as a confounder

Conclusion

This study demonstrated a direct relationship between serum uric acid concentration, and serum creatinine and urea levels; and also indicated that as glomerular filtration rate falls, uric acid levels increase as well. Moreover, serum creatinine levels were significantly higher in hypertensive males with raised SUA levels. Furthermore, serum uric acid levels varied directly with fasting blood sugar among male hypertensive participants. According to our findings, it could be suggested that serum uric acid levels may either modify renal function or itself be modified by renal impairment in hypertensive patients.

Further Research and Perspectives

The paradoxical relationship between uric acid and target organ pathologies represents an area for contemporary operational research following previous reports on their association from studies replicated in several ethnic populations, and also following the non-universal acceptance and inclusion of hyperuricaemia as part of cardiovascular disease risk factors. Few studies in this line have been carried out in Cameroon in particular and Africa as a whole, thus the validity or non-validity of such associations cannot be undoubtedly ascertained, hence the need for extensive, longitudinal, and multidisciplinary studies to investigate previous claims and hypotheses.

Author's Contributions

MTT and OPM conceived the study, defined the experimental design and intellectual content, and prepared and edited the manuscript. MTT carried out laboratory experiments while OPM and DAN performed clinical studies. MTT and DAN performed the literature search, and all authors participated in data acquisition and analysis, proof reading and approval of the final manuscript.

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Conflict of Interest

All authors disclose that there was no conflict of interest.

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