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Uric Acid Metabolism in a Sample of Egyptian Hypertensive Patients With Normal Kidney Function

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Abstract

Background: Hyperuricemia is commonly associated with hypertension. Also, it is well known to coincide with the metabolic syndrome but is still not recognized as a risk factor. So, **we aimed to** evaluate hyperuricemia among a sample of hypertensive Egyptians with normal renal function.

Methods: this study was performed on 303 hypertensive patients aged 30-69 years. Patients were divided into 2 groups according to the level of uric acid**: group 1** composed of 168 hypertensive hyperuricemic patient sand **group2** composed of 135 hypertensive normouricemic patients. All patients were subjected to complete medical history and detailed clinical examination including body mass index (BMI), complete blood count (CBC), serum creatinine, BUN, FBS, cholesterol, triglycerides, uric acid, sodium, potassium, urinary uric acid, urinary creatinine, urinary uric acid to creatinine ratio and fractional excretion of uric acid(FEUA).

Results: The overall prevalence of hyperuricemia was 55.4%. Uric acid correlated significantly with age ***(p<0.05).*** BMI was significantly higher in group1 than in group 2***(p<0.05),*** and there was a significant positive correlation between serum uric acid and BMI ***(p<0.01).***Serum triglycerides and cholesterol were significantly higher in group 1than in group 2 ***(p<0.05for both)*** denoting risky metabolic effects**.** Serum uric acid correlated significantly with systolic blood pressure ***(p<0.05),*** but not with diastolic blood pressure. No significant difference found between group 1 and group 2 as regards SBP, DBP or blood pressure control***(all p values>0.05).*** Serum uric acid found to correlate significantly (p***<0.001)*** with urinary uric acid, urinary creatinine and negatively with FEUA denoting early tubular defect of the kidney**.** Also, Urinary uric acid, urinary creatinine and urinary uric acid/creatinine ratio were higher in group 1than in group 2 ***(p values were<0.001, <0.001 and <0.05 respectively***). FEUA was found to be significantly lower in group 1 than in group 2 ***(p<0.01).*** We found, also, that serum sodium level was significantly higher in the hyperuricemic group than in the normouricemic group ***(p<0.001)*** denoting the role of Na^+ in the development of hypertension and defective renal excretion of uric acid.

Conclusion: We conclude that the incidence hyperuricemia in our sample of Egyptian hypertensive patients was (55.4%). Impaired renal clearance of uric acid occurs before deterioration of GFR. Serum uric acid should be measured in all cases of hypertension together with BMI, total cholesterol, triglycerides and should be treated to avoid consequent metabolic complications. Hypertensive patients with hyperuricemia should be warned strictly of high sodium diet.

Key words: Hyperuricemia- Hypertension- Kidney function- Metabolic syndrome.

Introduction

Hyperuricemia is commonly associated with hypertension ***(1).*** Serum uric acid was closely linked to the development of hypertension and that it might be a marker of susceptibility or an intermediate step in the pathway leading to hypertension***(2).***Also, it is well known that hyperuricemia coincides with the metabolic syndrome but is still not recognized as a risk factor. Subjects with hyperuricemia were 3.5 times more likely to develop the metabolic syndrome than subjects with normal uric acid levels ***(3)*** .So; we aimed to investigate the prevalence of hyperuricemia among a sample of hypertensive Egyptians and to evaluate uric acid metabolism and excretion among hypertensive subjects with normal renal functions.

Patients and Methods

This cross sectional study was performed on 303 hypertensive patients selected from the

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outpatient clinic of Electricity hospital and Ain Shams University hospital. Hypertension is defined by the sixth report of the Joint National Committee on Prevention , Detection , Evaluation, and Treatment of High Blood Pressure **(JNCVI)** and the World Health Organization-International Society of Hypertension (WHO-ISH), (i.e. systolic BP≥140mmHg, diastolic BP≥ 90mmHg).

Patients were divided into 2 groups according to the level of uric acid. Group 1, composed of hypertensive hyperuricemic patients. Hyperuricemia is defined as serum uric acid level ≥7 mg/dl (in ♂) or ≥6.0 mg/dl (in ♀) *(4)*. Group 1 was found to be composed of 168 patients. Group2, composed of hypertensive normouricemic patients (found to be 135 patients).

All studied patients were subjected to complete medical history and detailed clinical examination including body mass index (BMI).Estimated Glomerular filtration Rate (eGFR) was done using the MDRD equation recommended by the national kidney foundation to ensure normal kidney function.

(GFR=170 $\times SCr^{-0.999} \times SUN^{-0.170} \times SAlb + 0.318 \times age^{-0.176}$ $\times 1.180$ if black or 0.762 if female. (ml/minute/1.73m²) =100-130 ml/minute/1.73m²).

Routine laboratory test including complete blood count (CBC), serum creatinine, blood urea nitrogen, serum fasting blood sugar (FBS), serum cholesterol, serum triglycerides, serum uric acid, serum sodium, serum potassium, urinary uric acid, urinary creatinine and urinary uric acid /creatinine ratio were performed for all cases.

Fractional excretion of uric acid (FEUA) was calculated by the standard formula

FEUA = Urinary uric acid x Plasma creatinine / Plasma uric acid X Urinary creatinine.

Exclusion criteria:

Patients younger than 30 years old or older than 60 years, patients having eGFR<90ml/minute/1.73m², patients taking medications known to increase or decrease the level of uric acid in the urine and patients of diabetes mellitus were excluded from the study.

Statistical Methods:

Data were analyzed sing an IBM personal computer, using statistical package for special science (SPSS) version14.

Quantitative data were expressed as mean± SD while qualitative data were expressed as number and percentage. Chi-square test (or Fisher's exact test when appropriate) was used for comparison of qualitative variables among different groups. Student t test of two independent samples was used for comparison of quantitative variables. Pearson correlation coefficient was used for testing association between different parametric variables. Spearman correlation coefficient was used to for testing association between different non-parametric variables.

P value >0.05was considered as insignificant, P<0.05was considered significant and P<0.01was considered highly significant.

Results

In our study we found that the prevalence of hyperuricemia in the studied hypertensive patients was 55.4%. We found that hyperuricemia was present in 46.4% of patients with controlled blood pressure and in 53.6% of patients with uncontrolled blood pressure.

As in ***table 4,*** it has been found that uric acid correlated significantly with age ***(p<0.05),*** BMI***(p<0.01).*** When comparing group1 with group 2***(table 2),*** BMI was statistically significantly higher in group 1***(p<0.05).*** Also, regarding serum triglycerides and serum cholesterol, it was significantly higher in group 1than in group 2 ***(p<0.05)*** (table 3).Serum uric acid was significantly correlated with systolic blood pressure ***(p<0.05)*** but not with diastolic blood pressure ***(table 3).*** There was no significant difference between group 1 and group 2 as regard SBP, DBP or blood pressure control. We found, also, that serum sodium level was significantly higher in the hyperuricemic group than in the normouricemic group ***(p<0.001) (table 3).***

As in Table 3 shows also that there was significantly higher urinary uric acid ***(p<0001),*** urinary creatinine ***(p<0001),*** urinary uric acid /creatinine ratio ***(p<0.05)*** and significantly lower (FEUA)***(p<0.01)***in group 1 than in group 2.

Serum uric acid was significantly correlated to urinary uric acid ***(p<0.001),*** urinary creatinine ***(p<0.001)*** and negatively correlated to fractional excretion of uric acid ***(p<0.001) (table 4).***

DISCUSSION

Uric acid is the final breakdown product of purine degradation in humans. Hyperuricemia results from increased production, decreased exertion or a combination of both ***(5).***

Prevalence of hyperuricemia:

In our study we found that the ***prevalence*** of hyperuricemia in our hypertensive patients was as high as 55.4%.In one study done on 1999, prevalence of hyperuricemia in hypertensive patients was 40.3% ***(6),***while in Pakistan, for example, hyperuricemia was found in 37.4% of hypertensive patients ***(7).*** **Schmidt et al.** ***(8)***showed that hyperuricemia was found more frequently in hypertensive subjects (20.1%) than in non-hypertensive subjects (6.7%), and hypertension was found more frequently in hyperuricemic subjects (60.7%) than in non-hyperuricemic subjects (30.5%).Studies from the 1950s and 1960s showed the prevalence of hyperuricemia in hypertensive patients is between 20 and 40% ***(9).***Variability of incidence was attributed to inclusion of patients with secondary hypertension in some reports and to weakening of the relationship between uric acid and hypertension with age***(10).*** In the current study, uric acid correlated significantly to ***age (p<0.05)***. This comes in agreement with studies which found significant positive correlation between serum uric acid and age. ***(11,12).***

In our study, there was no significant difference found between group 1 and group 2 as regard SBP, DBP or blood pressure control. We found that serum uric acid significantly correlated to systolic ***blood pressure (p<0.05)*** but not to diastolic blood pressure. This comes in agreement with other studies which demonstrated a linear relationship between serum urate levels and systolic blood pressure ***(13,14,15).***We found, also, that hyperuricemia was present in 46.4% of patients with controlled blood pressure and in 53.6% of uncontrolled blood pressure. **Cannon et al.(1)** reported that hyperuricemia was present in 25% of untreated hypertensive subjects, 50% of subjects taking diuretics, and more than 75% of subjects with malignant hypertension**.**

- ***Hypertension hyperuricemia relationship:***

Hyperuricemia is known to be strongly associated with hypertension ***(1).***Mechanism by which uric acid plays a pathogenic role in hypertension is not completely clear but it includes reduction of endothelial nitric oxide and stimulation of renin expression ***(16).*** Hyperuricemia is associated with deleterious effects on endothelial function, platelet adhesion and aggregation, in addition to oxidative metabolism ***(17).***Hypertension, also, exerts mechanisms that perpetuate hyperuricemia .Hypertension decreases renal blood flow which stimulates urate reabsorption, micro vascular (capillary) tissue ischemia leads to increased production of lactates which blocks urate secretion in the proximal tubules, ischemia, also, increases the production of xanthine oxidase and increases purine breakdown leading to increased urate production and more hyperuricemia***(18).***

Another factor which aggravates both hypertension and hyperuricemia and which should be highlighted here is increased **salt sensitivity** due to renal ischemia which stimulates tubular sodium reabsorption on an attempt to relieve ischemia on the expense of blood pressure. Meanwhile, uric acid and $\mathbf{Na^+}$ reabsorption in the proximal tubules appear to be positively associated. This process is enhanced by the interaction between alpha-1 adrenoreceptor stimulation and angiotensinII that takes place at nephron level. AngiotensinII augments uric acid reabsorption and reduces renal uric acid excretion leading to more hyperuricemia ***(19,20).*** In our study, Na^+ was significantly higher in group1 than in group 2 ($p<0.001$) .So, we recommend low sodium diet in hypertensive subjects especially when they are hyperuricemic.

- ***Hyperuricemia and dyslipidemia:***

In our study ***BMI*** was significantly higher in group1 than in group 2 ***(p<0.05***) and there was a significant positive correlation

between serum uric acid and BMI ***(p<0.01)*** but the mean BMI remained within normal range in both groups**.** Serum ***triglycerides and total cholesterol*** were found to be significantly higher in group1 than in group2 ***(p<0.05 for both)*** but both of them were above the normal reference range.

Previous studies reported that obesity and central body fat distribution were associated with hyperuricemia ***(21,22,23).*** Association between obesity and uric acid can be mediated by leptin (obesity gene product).It was suggested that leptin could be a pathogenic factor responsible for hyperuricemia in obese patients ***(24,25).***

Lipid metabolic disorder is usually coupled with hyperuricemia, because increased lipoprotein esterase levels decreases clearance of uric acid. Meanwhile, hyperuricemia reduces triglycerides decomposition and increases triglycerides levels by repressing lipoprotein lipase activity ***(2)***. Many studies found that serum triglyceride was markedly associated with hyperuricemia ***(26,27,28).*** Increased serum uric acid promotes oxygenation of low density lipoproteins, cholesterol and facilitates lipid peroxidation with production of oxygen free radicles which leads to progression of atherosclerosis ***(29).*** Hyperuricemia is commonly observed in the **metabolic syndrome** ***(30)*** as well as insulin resistance ***(31).*** The kidney also might be at risk through activation of the renin angiotensin system and deposition of lipids in the renal parenchyma resulting in increased interstitial pressure ***(32).***

In this situation we advise measurement of uric acid and total lipid profile for early treatment of these metabolic features..

- ***Uric acid metabolism in hypertension:***

In our study, there was statistically significant higher urinary uric acid ***(p<0.001),*** urinary creatinine ***(p<0.001),*** urinary uric acid/creatinine ratio ***(p<0.05)*** and lower fractional excretion of uric acid **(FEUA)*****(p<0.05)***in group 1 than in group 2. Serum uric acid was significantly correlated to urinary uric acid ***(p<0.001),*** urinary creatinine ***(p<0.001),*** and negatively correlated to fractional excretion of uric acid ***(p<0.001)***. These results denote early renal tubular trouble that caused lowering of the FEUA in spite of apparently normal kidneys by eGFR ***(33,34).***

Conclusion:

We conclude that the incidence hyperuricemia in our sample of Egyptian hypertensive patients was (55.4%).Impaired renal clearance of uric acid occurs before deterioration of GFR. Serum uric acid should be measured in all cases of hypertension together with BMI, total cholesterol, triglycerides and should be treated to avoid consequent metabolic complications. Hypertensive patients with hyperuricemia should be warned strictly of high sodium diet.

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Table 1: Baseline characteristics of patients

	Mean	Standard Deviation
Age	44.35	±4.5
Body mass index	27.13	±3.5
Systolic blood pressure	147.7	±12.36
Diastolic blood pressure	91.47	±7.25
Hypertension duration	37.37	±30.88
Hemoglobin	13.15	±1.52
White cell count	6.77	±1.64
Platelets	245.93	±54.10
Serum Urea	33.98	±9.94
Serum Creatinine	1.01	±0.13
Serum Cholesterol	256.64	±49.65
Serum Triglycerides	157.07	±57.14
Serum Na	136.77	±5.39
Serum K	4.76	±3.93
Fasting blood sugar	99.90	±39.41
Serum Uric acid	7.14	±1.58
Urinary uric acid (mg %)	36.48	±21.43
Urinary creatinine (mg %)	74.42	±44.18
Urinary uric acid /Urinary creatinine Ratio	0.59	±0.45
Uric acid excretion	9.11	±7.44

Table2:shows comparison of general characteristics between group1 and group2

Variables	Group 1 (N=168) Mean ±SD	Group2 (N=135) Mean ±SD	t test	P value
Age	44.63 ± 4.24	44.01 ± 4.93	-1.164	0.246
BMI	27.58 ± 3.37	26.56 ± 3.58	-2.541	0.012
Systolic BP	147.86 ± 13.05	147.56 ± 11.49	-2.140	0.831
Diastolic BP	91.01 ± 7.04	92.04 ± 7.49	1.224	0.222
HTN duration	37.64 ± 28.19	37.64 ± 34.03	0.140	0.889

Table 3:comparison of laboratory data between group 1 and group 2

Variables	Group 1 (N=168) Mean± SD	Group2 (N=135) Mean± SD	t test	P value
Hemoglobin	12.9 ± 1.53	13.47 ± 1.45	3.337	0.001
WBC	7.11 ± 1.34	6.33 ± 1.86	-4.093	0.001
Platelets	245.77 ± 53.19	246.13 ± 55.41	0.057	0.954
Serum urea	35.41 ± 9.39	32.21 ± 10.35	-2.820	0.005
Serum Creatinine	1.02 ± 0.13	1.00 ± 0.12	-0.953	0.341
Serum Cholesterol	263.09 ± 48.43	248.61 ± 50.16	-2.546	0.011
Serum triglycerides	162.91 ± 64.57	149.81 ± 45.46	-2.068	0.039
Serum Na	138.5 ± 4.14	134.61 ± 5.98	-6.415	0.001
Serum K	5.27 ± 5.22	4.12 ± 0.3	-2.840	0.005
FBS	100.31 ± 10.01	99.4 ± 58.1	-0.180	0.858
Serum uric acid	8.37 ± 0.75	5.61 ± 0.83	-30.379	0.001
Urinary uric acid	45.07 ± 21.89	25.79 ± 15.19	-9.025	0.001
Urinary creatinine	84.99± 41.79	61.05 ±43.63	-4.841	0.001
UUA/UC Ratio	0.65 ± 0.51	0.52± 0.36	-2.482	0.014
FEUA	7.88± 5.99	10.64± 8.71	3.137	0.002

Table 4: correlation of uric acid with different parameters

	R value	**P value**
Age	0.130	0.023
BMI	0.148	0.010
SBP	0.140	0.015
Serum urea	0.218	0.001
Serum creatinine	0.146	0.011
Urinary uric acid	0.512	0.001
Urinary creatinine	0.355	0.001
FEUA	-0.235	0.001