Original Article

Serum Uric Acid and Salt Sensitivity in the Normotensive Population: An Iranian Sample

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ABSTRACT

Background: It is not clear whether the serum uric acid level is independently associated with the long-term incidence of hypertension. The aim of this study was to assess the association between serum uric acid and salt sensitivity in an Iranian normotensive population.

Methods: This cross-sectional study was conducted at the Cardiovascular Research Institute, Isfahan University of Medical Sciences, from July 2014 to October 2014. A group of 140 eligible healthy volunteers aged between 20 and 40 years with a normal blood pressure was enrolled in this study. After the determination of the baseline mean blood pressure and serum uric acid level, salt sensitivity was determined in all the subjects according to a protocol described by Weinberger and Fineberg via the infusion of normal saline and furosemide in 2 consecutive days. Blood pressure was determined before and 2 hours after these interventions. All the data were analyzed using the Student *t*-test, the χ^2 test, and a multiple logistic regression model.

Results: The average age of the study population was 25.73±3.35 years, and the mean body mass index was 23.1±2.9 kg/m^2. According to the definition for salt sensitivity, 56 (42.7%) of the participants were sensitive and 75 (57.3%) were not sensitive to salt. Thirty-nine (29.8%) of the participants were hyperuricemic, 20 (51.3%) of whom were salt sensitive. Among the normouricemic participants, 49 (53.3%) were salt sensitive. These differences were not statistically significant between the salt-sensitive and salt-insensitive groups (*P*=0.23). There was no association between hyperuricemia and salt sensitivity even after adjustments were made for the demographic and anthropometric variables (OR=0.70 and 95 CI=0.29 to 1.68).

Conclusions: We did not find an association between serum uric acid and salt sensitivity among our young Iranian normotensives. ***(Iranian Heart Journal 2018; 19(4): 26-32)***

KEYWORDS: Hypertension, Salt sensitivity, Hyperuricemia

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Received: March 12, 2018 **Accepted:** June 18, 2018

Cardiovascular diseases comprise the most common causes of death in the world. The most common form of cardiovascular diseases is hypertension (HTN), which is present in approximately 28.6% of the adult population.[1] HTN markedly increases the risk of myocardial infarction, stroke, peripheral vascular disease, and end-stage renal disease.[2,3]

Dietary NaCl, termed "salt", has long been deemed a major contributing environmental factor in the pathogenesis of HTN.[4] There is some evidence that the increased prevalence of HTN is a recent event in human history, and there is a correlation between changes in the diet and industrialization. Dahl and Tobian suggested that a key nutritional factor that may account for the increased prevalence of HTN in industrialized societies is dietary sodium intake.[5,6]

Primitive societies, such as the Yanomami, whose populations ingested a very small amount of sodium, did not have HTN.[7] The sodium content of early hunter-gatherers of the Palaeolithic period was also extremely low and has been estimated to be only 690 mg/d, equivalent to 30 mEq Na.[8] In contrast, the average sodium intake in the current American diet averages 4000 mg/d (170 mEq Na or approximately 10 g of NaCl).[9,10] Although individuals with normal kidneys may be able to excrete the increased sodium content without an alteration in their systemic blood pressure (BP), there is some evidence that individuals who develop essential HTN have a relative defect in their ability to excrete sodium.[11]

It is clear that BP responses to dietary salt intake vary among individuals. According to the degree of these responses, individuals can be grouped into categories of salt sensitivity and salt resistance. It has been speculated that the sudden increase in sodium content in the diet of an industrialized population will unmask those individuals with the physiological renal defect and, thereby, precipitate the development of HTN.[4]

Hyperuricemia (uric acid ≥7 mg/dL) is a common metabolic disorder due to the decreased secretion of nucleotides catabolism (urate), with a prevalence rate of 21.4% in the adult population of the United States of America.[1] Given that hyperuricemia induces primary renal arteriolar lesions, it has been hypothesized that chronic hyperuricemia may also induce salt sensitivity.[13] Whereas an elevated serum uric acid may be advantageous for maintaining BP under low-salt dietary conditions, the induction of chronic salt sensitivity would be expected to result in HTN in modern society with its high-salt diet. It is of interest that hyperuricemia predicts the development of HTN and is strongly linked to cardiovascular diseases.[14]

Investigators now present a hypothesis that the development of salt sensitivity in humans may be related to environmentally driven mutations of the urate oxidase (uricase) gene, which occurred during the Miocene.[15] The aim of this study was to assess the association between serum uric acid and salt sensitivity in the normotensive population.

METHODS

This cross-sectional study was conducted at the Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran, from July 2014 to October 2014. A wide range of materials from brochures to posters was used to find potential volunteers from the community. A total of 140 participants volunteered to take part in our cross-sectional study. The eligibility criteria included willingness to participate in the study; age 18 years and older; and a normal BP, defined as a systolic BP below 140 mm Hg and a diastolic BP below 90 mm Hg based on 3 screening visits of 1 week apart. The individuals were excluded based on the following criteria: a history of HTN; a history of special diet including low fat and salt diets; a history of taking antihypertensive medications, oral

contraceptives, and nonsteroidal anti-inflammatory drugs; and a history of myocardial infarction, cardiac failure, cerebrovascular accidents, and renal failure.

The study protocol was approved by the Ethics Committee of the Cardiovascular Research Institute. Written informed consents were obtained from each participant for data collection and intervention.

Trained staff collected information on demographic characteristics—including age, gender, family medical history of HTN or coronary artery disease, and regular physical activity—at baseline. In addition, anthropometric measurements of weight, height, and waist were obtained with the individual in minimal clothing. The body mass index (BMI) was calculated as weight (kg) by height squared (cm).

Venous blood samples after fasting for at least 8 hours were taken for the measurement of the levels of serum blood urea nitrogen (BUN), creatinine (Cr), uric acid, sodium (Na), and potassium (K). Plasma measurements were assessed using commercially available kits (Pars Azmoun, Iran). Based on their serum uric acid level, measured via the uricase ESMT method (Pars Azmoun, Iran), the subjects were categorized into 2 groups: hyperuricemia (serum uric acid concentration>7.0 mg/dL) and normal uric acid (≤7 mg/dL).

Study Design

The current study was conducted in 2 days. On the first day of the study, the individuals were admitted at 8 AM and were put on a low-calorie and low-sodium diet. Venous blood samples were obtained, anthropometric measurements were calculated, and questionnaires were filled out by trained staff. Two hours after the admission, 3 measurements of BP were obtained at 5-minute intervals and their mean was recorded as the baseline BP. BP was obtained by a single trained staff member for each participant using an automated mercury sphygmomanometer with the individual in the sitting position and 5 minutes of rest. All the participants were also asked to avoid consuming alcohol, tea, or coffee; performing physical exercise; and smoking for at least 1 hour prior to admission. The mean arterial pressure (MAP) was calculated as [(2*diastolic) + systolic]/3 and reported for each measurement.

After the baseline BP was obtained, 2 liters of normal (0.9%) saline were administered intravenously over 4 hours (500 mL/h). Two hours after the normal saline infusion, BP was obtained and the post-saline MAP was calculated. Following the intervention, the participants were discharged home and arrangements were made for them to return to the research institute the next morning.

To ensure compliance with the study protocol, the individuals were required to eat pre-packaged foods that were prepared according to the protocol (low-carbohydrate, low-fat, and low-sodium) and were instructed to avoid any foods that were not provided by the study staff. The participants were also followed up on the night by telephone to evaluate any potential side effects and to ensure their adherence to the study dietary protocol.

On the following day, the participants were again admitted at 8 AM and BP was measured. Sodium and volume depletion was then induced with a 10-mmol sodium diet and the administration of 3 doses of oral furosemide (40 mg each dose, at 10 AM, 2 PM, and 6 PM). Two hours after the completion of the last dose of furosemide, BP was again measured according to the study protocol. The MAP after sodium and volume depletion was compared with the post-saline MAP.

The individuals that demonstrated a minimum decrease of 10 mm Hg in their MAP were defined as “salt sensitive”, and those with a maximum decrease of 10 mm Hg in their MAP were categorized as “salt insensitive” including both salt-resistant (ΔMAP≤6 mm Hg) and intermediate-resistant (ΔMAP=6–10 mm Hg) with respect to sodium sensitivity.

Data Analysis

All the data were analyzed using the SPSS software, version 15 (SPSS Inc, Chicago, IL, USA). A *P* value equal to or less than 0.05 was considered statistically significant for all the analyses. The normality of the distribution of the variables was examined using the Kolmogorov–Smirnov test, which showed that the variables were normally distributed. The Student *t*-test was applied for the continuous variables and the χ^2 test for the discrete variables. A multiple logistic regression model was carried out to examine the association between salt sensitivity and the uric acid level; the model was adjusted based on age, sex, the BMI, and a family history of HTN. Odds ratios (ORs) were reported with the corresponding 95% confidence intervals (CIs). The goodness of fit was calculated with the Hosmer–Lemeshow statistic.

RESULTS

Of the total of 140 participants, 9 individuals were excluded from the study because they failed to adhere to the study dietary protocol or failed to complete the intervention. The average age of the study population was 25.73±3.35 years, and the mean BMI was 23.1±2.9 kg/m^2. According to the definition for salt sensitivity, 56 (42.7%) of the participants were sensitive and 75 (57.3%) were not sensitive to salt. Among the males, 45 (80.4%) were salt sensitive and 55 (73.3%) were salt insensitive. The other baseline characteristics and clinical data are presented in Table 1. Based on our results in Table 1, there were no statistical differences between the sensitive and insensitive groups to salt. Hyperuricemia was detected in 39 (29.8%) of the participants. Among the hyperuricemic subjects, 20 (51.3%) were salt sensitive, according to the defined criteria. Among the normouricemic participants, 49 (53.3%) were salt sensitive. The differences between the salt-sensitive and salt-insensitive groups were not statistically significant (*P*=0.23), meaning that there was no association between salt sensitivity and the level of serum uric acid in our study subjects. For a better evaluation of the risk of salt sensitivity in the hyperuricemic subjects, we determined the ORs of salt sensitivity for hyperuricemia. The analysis of the multiple logistic regression (Table 2) showed no significant relationship between hyperuricemia and salt sensitivity, even when it was adjusted based on age (OR=0.56 and 95% CI=0.25 to 1.25) and based on age, sex, the BMI, and a family history of HTN (OR=0.70 and 95% CI=0.29 to 1.68). The results from the Hosmer–Lemeshow test showed a good fit for the multiple logistic regression models (χ^2=6.50 and *P*=0.48 for the age-adjusted model and χ^2=11.80 and *P*=0.16 for age, the BMI, and a family history HTN for the HTN-adjusted model).

Table1. Baseline characteristics and clinical data of the study population

Variable	Salt Insensitive (N= 75)	Salt Sensitive (N= 56)	*P*
Sex (male) (%)	55 (73.3)	45 (80.4)	0.349[1]
Age, y (mean ± SD)	25.23 ± 4.68	26.36 ± 6.91	0.272[2]
Family history of hypertension (%)	22 (29.3)	16 (28.6)	0.995[1]
Family history of coronary artery disease (%)	7 (9.3)	6 (10.7)	0.770[1]
Regular physical activity (%)	30 (40.0)	19 (33.9)	0.522[1]
Weight (mean ± SD)	68.21 ± 13.05	71.16 ± 12.33	0.193[2]
Body mass index (mean ± SD)	22.75 ± 2.71	23.71 ± 2.93	0.057[2]
Waist circumference (mean ± SD)	81.54 ± 8.96	82.86 ± 8.41	0.404[2]
uric acid (mean ± SD)	6.91 ± 6.57	6.42 ± 1.56	0.597[2]
Na (mean ± SD)	140.30 ± 2.42	140.46 ± 2.39	0.699[2]
K (mean ± SD)	4.38 ± 0.53	4.34 ± 0.34	0.662[2]
BUN (mean ± SD)	12.56 ± 3.72	13.73 ± 3.63	0.077[2]
Cr (mean ± SD)	0.92 ± 0.12	0.96 ± 0.10	0.067[2]

[1]*P* values obtained from the χ^2 test and [2] *P* values obtained from the *t*-test

Table 2. Crude and adjusted multiple logistic regression analyses of salt sensitivity and serum uric acid

Variable	OR (95% CI)	*P*
Crude	0.59 (0.27-1.27)	0.17
Age-adjusted	0.56 (0.25-1.25)	0.16
Fully adjusted*	0.70 (0.29-1.68)	0.43

*Fully adjusted: age, sex, the body mass index, and a family history of hypertension

DISCUSSION

The results of the present study revealed hyperuricemia in 29.8% of the participants. Among the hyperuricemic participants, 51.3% were salt sensitive. Among the hyperuricemic subjects, 20 (51.3%) were salt sensitive, according to the defined criteria. Among the normouricemic participants, 49 (53.3%) were salt sensitive. Moreover, the findings showed no association between salt sensitivity and the level of serum uric acid in the participants even after adjustments were made in terms of age, the BMI, and a family history of HTN.

Although the relationship between sodium intake and HTN is well-established, its relationship with uric acid is controversial. It has been demonstrated in some rat models that BP increases in consequence of hyperuricemia in the context of a low-sodium diet. Some rat models have also supported the notion that uric acid causes the upregulation and activation of the epithelial sodium channels in the nephron.[16,17] In a study with a rat model of hyperuricemia, Johnson and colleagues[18] demonstrated a uric acid-dependent BP elevation and posited a biological mechanism whereby uric acid could lead to similar BP elevations in humans. There is evidence for this hypothesis. Firstly, renal vasoconstriction occurs when there is an inhibition of the nitric oxide pathway and an activation of the renin–angiotensin system (RAS); this resulting elevation in BP is reversible by decreasing uric acid levels. A recent report demonstrated that the uric acid level was associated with a lower basal renal plasma flow and blunted renal vasoconstriction, which is typically seen with angiotensin II infusion during high-salt balance, lending support to the hypothesis that uric acid may activate the renal RAS directly.[19] Secondly, vascular smooth muscle cell proliferation and inflammation as a result of uric acid may lead to irreversible damage to small renal vessels, leading to the persistence of HTN and salt sensitivity.[20]

Some experimental studies have demonstrated a rise in BP as a result of a high-salt diet (ie, salt sensitivity) only in previously hyperuricemic rats, indicating that hyperuricemia in rats can induce salt sensitivity. This finding is consistent with other models in which salt sensitivity can be induced as a consequence of the development of pre-glomerular arteriolar disease.[18,21]

Not only does uric acid predict the development of HTN, but also a recent study has suggested that elevated uric acid is much more common in the new-onset hypertensive patient than was originally believed. In a study of new-onset HTN in adolescents, 89% of children with essential HTN had a uric acid level of above 5.5 mg/dL.[22]

The possible effect of age on the association between uric acid and HTN was suggested previously in an article by Sundstrom et al,[23] who noted a 13% increase in risk for each 1.0-mg/dL increment in uric acid (mean age=48.7 y), compared with a 20% increase per 1.0 mg/dL in a study by Taniguchi et al[24] (mean age=41 y) and a 23% increase per 1.0 mg/dL in a study by Josaa et al[25] (mean age=36 y). Therefore, hyperuricemia may affect the control of BP by renal mechanism and elevated uric acid levels in conjunction with the exaggeration of salt sensitivity may induce HTN in adulthood.

In contrast, our results determined no association between uric acid and salt sensitivity, which is compatible with a study by Forman et al,[26] who found no independent association between the uric acid level and the risk for the incidence of HTN among older

men. In addition, a previous study showed that—at least in the short term—uric acid and BP might change significantly in opposite directions.[27]

The most notable difference between our study and the previous ones is the age of the populations and the evaluation of the association between elevated uric acid levels and the risk of salt sensitivity in a healthy normotensive young adult. The limitation of the current study is that it was conducted on a small sample size of normotensive individuals. Consequently, further studies with larger sample sizes on hypertensive patients are recommended.

CONCLUSIONS

In many patients, hyperuricemia is associated with the development of HTN. Nonetheless, whether hyperuricemia has a causal role or whether it only indicates a complication of HTN and the use of drugs remains controversial. Our study results suggested that hyperuricemia should not be considered a risk factor for the salt-sensitive elevation of BP and could not be a useful marker for the screening of young males for salt sensitivity. We would recommend that cohort studies be performed to determine the relationship between the uric acid level and the natural course of HTN.

Funding/Support

This study was financially supported by the Cardiovascular Research Institute, Isfahan University of Medical Sciences (grant No.: 89107).

Acknowledgments

The authors wish to thank all the study volunteers and the staff of the Cardiovascular Research Institute, Isfahan University of Medical Sciences, for their kind cooperation.

Conflict of Interest

All the authors declared no conflict of interest.

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