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Original Report

Title:

Association between hypouricemia and reduced kidney function: a cross-sectional population-based study in Japan

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Abstract

Background: Hypouricemia, conventionally defined as a serum uric acid level of ≤2 mg/dL, is considered a biochemical disorder with no clinical significance. However, individuals with renal hypouricemia have a high risk of urolithiasis and exercise-induced acute kidney injury, both of which are risk factors for reduced kidney function.

Methods: To test the hypothesis that individuals with hypouricemia would be at a higher risk of reduced kidney function, we conducted a population-based cross-sectional study using data from the Specific Health Checkups and Guidance System in Japan. Logistic analysis was used to examine the relationship between hypouricemia and reduced kidney function, defined as an estimated glomerular filtration rate <60 mL/min/1.73 m^2.

Results: Among 90,710 men (mean age, 63.8 years) and 136,935 women (63.7 years), 193 (0.2%) and 540 (0.4%) were identified as having hypouricemia, respectively. The prevalence of hypouricemia decreased with age in women (P for trend < 0.001), but not in men (P for trend = 0.24). Hypouricemia was associated with reduced kidney function in men (odds ratio, 1.83; 95% confidence interval, 1.23–2.74), but not in women (0.61; 0.43–0.86), relative to the reference category (i.e., serum uric acid levels of 4.1-5.0 mg/dL) after adjusting for age, drinking, smoking, diabetes, hypertension, hypercholesterolemia, obesity, and history of renal failure. Sensitivity analyses stratified by diabetic status yielded similar results.

Conclusions: This study is the first to provide evidence that hypouricemia is associated with reduced kidney function in men. Further research will be needed to determine the long-term prognosis of individuals with hypouricemia.

Introduction

Little is known about the clinical epidemiology of hypouricemia due to its low prevalence in the general population. Hypouricemia is conventionally defined as a serum uric acid concentration of ≤ 2 mg/dL [1], and occurs in about 2% of hospitalized patients and less than 0.5% of the general population [2]. It remains unclear whether age and sex affect its prevalence, and the long-term prognosis of individuals with hypouricemia has yet to be clarified. Uric acid is one of the most important antioxidants in human plasma [3-5] and is positively correlated with lifespan in primates [6]. Individuals with hypouricemia are hypothesized to be at increased risk of atherosclerotic diseases and cancer, due to the decreased antioxidant potential resulting from lower uric acid levels [3]. Yet, there exists no clinical evidence supporting this hypothesis.

In general, hypouricemia is considered a biochemical disorder with no clinical significance, other than serving as a marker for underlying diseases [7]. However, a recent study reported that subjects having the common nonsense mutation, W258X, which is responsible for renal hypouricemia, showed significantly reduced renal function independently of age, sex, BMI, hypertension, and serum uric acid levels [8]. In addition, renal hypouricemia is known to be associated with two complications, acute kidney injury (AKI) [9,10] and nephrolithiasis [10,11]. Because both AKI and urolithiasis are risk factors for reduced kidney function [12,13], we hypothesized that individuals with hypouricemia may be at greater risk of reduced kidney function.

Here, we present the results of a large cross-sectional study reporting the gender specificity of age-related prevalence of hypouricemia, and its association with reduced kidney function in the general Japanese population.

Methods

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Study population

This cross-sectional study used data obtained from the Japanese specific health check and guidance system (SHC) in 2008. The SHC has been described elsewhere [14,15]. Briefly, the SHC is a new health-care strategy aimed at early diagnosis and intervention for metabolic syndrome, and was initiated by the Japanese government in 2008. Participants answer a self-administered questionnaire covering their medical history, smoking habits, alcohol intake, and exercise pattern. Trained staff then measures the height, weight, blood pressure, and waist circumference of each participant, after which serum and spot urine samples are collected. Participants diagnosed with metabolic syndrome are obligated to receive repeated lifestyle guidance over a 6-month period after an annual health examination.

Twenty-four prefectures (Hokkaido, Miyagi, Yamagata, Fukushima, Ibaraki, Tochigi, Tokyo, Saitama, Kanagawa, Niigata, Nagano, Ishikawa, Gifu, Osaka, Okayama, Tokushima, Kochi, Fukuoka, Saga, Nagasaki, Oita, Kumamoto, Miyazaki, and Okinawa) that agreed with our study purpose were included in the present analysis. Data were sent to and verified by an independent data center (NPO Japan Clinical Research Support Unit; Tokyo, Japan). Anonymity of all participants was maintained, and the study was conducted in conformity with the Declaration of Helsinki, Japanese privacy protection laws, and ethical guidelines for epidemiological studies published by the Ministry of Education, Science and Culture, and the Ministry of Health, Labour and Welfare. The study protocol was approved by the ethics committee of Fukushima Medical University (No. 1485).

Hypouricemia

Serum uric acid levels were measured by an enzymatic method and categorized as ≤ 2, 2.1 - 3.0, 3.1 - 4.0, 4.1 - 5.0, 5.1 - 6.0, 6.1 - 7.0, and > 7 mg/dL, with the middle category (4.1 - 5.0 mg/dL) set as the reference category. Hypouricemia was defined as a serum uric acid level ≤ 2 mg/dL [1].

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Kidney Function

Serum creatinine levels were measured by an enzymatic method. Estimated glomerular filtration rate (eGFR) was obtained by using the Japanese GFR equation [16]. The main outcome was reduced kidney function, defined as eGFR <60 mL/min/1.73 m^2.

Other Covariates

Information regarding current smoking, alcohol, and exercise habits; history of stroke, heart disease; and use of medications for diabetes mellitus, hypertension, or hypercholesterolemia was collected from the questionnaire. Information regarding history of renal failure was collected using the questionnaire, which included the following question: 'Have you ever been told by a doctor that you have chronic renal failure or have you ever received treatment for chronic renal failure (dialysis)?'. If the answer was "yes," the participant was considered to have a history of renal failure. A history of renal failure mainly consists of a past history of AKI and/or chronic kidney disease stage 4 or 5. A current smoker was defined as an individual who has smoked a total of 100 or more cigarettes, or smoked for 6 months or longer and has been smoking, for the last 1 month. A daily drinker was defined as an individual who drinks alcohol every day.

Body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2). Obesity was defined as a BMI ≥25 kg/m^2, according to the Japan Society for the Study of Obesity [17]. The value of hemoglobin A1c (HbA1c) was estimated as a National Glycohemoglobin Standardization Program equivalent value calculated with the following equation: HbA1c (%) = HbA1c (Japan Diabetes Society) (%) + 0.4% [18]. Diabetes was defined in accordance with American Diabetes Association guidelines as a fasting glucose concentration of 126 mg/dL or higher, HbA1c 6.5% or higher, or self-reported use of anti-hyperglycemic drugs [19]. Hypertension was defined as the

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use of antihypertensive medications, a systolic blood pressure ≥140 mmHg and/or a diastolic blood pressure ≥90 mmHg, or both. Hypercholesterolemia was defined as the use of cholesterol-lowering medications, a low-density lipoprotein cholesterol level ≥140 mg/dL, or both. Proteinuria was defined by a dipstick urinalysis score of 1+ or greater (equivalent to ≥30 mg/dl), because of poor discrimination between negative and trace positive dipstick readings [20].

Statistical Analyses

Data were analyzed separately by gender, and presented as mean (standard deviation) or median (interquartile range) for continuous variables and percent for categorical variables. A comparison of clinical characteristics by serum uric acid levels was performed using the chi-square test for categorical data, and analysis of variance or the Kruskal-Wallis test for continuous variables. For multiple comparisons, Fisher's exact test with Bonferroni correction, Dunnett's parametric multiple-comparison test, or Steel's nonparametric multiple comparison test [21] was used to compare the reference category to all other categories. Prevalence of hypouricemia was stratified by age and eGFR; age categories were: 40-49, 50-59, 60-69, and 70-74 years, and eGFR categories were: ≤15, 15-29, 30-44, 45-59, 60-89, and >90 ml/min/1.73 m^2 (in accordance with the definition in Kidney Disease: Improving Global Outcomes [KDIGO]) [22].

Logistic regression was used to assess the relationship between hypouricemia and reduced eGFR after adjusting for a priori identified covariates. Four levels of multivariable adjustment were examined: (1) unadjusted; (2) Model 1, which included age (per 10-year increase), daily drinker, current smoker, hypertension, diabetes mellitus, and hypercholesterolemia; (3) Model 2, which included all covariates in Model 1 and obesity; and (4) Model 3, which included all covariates in Model 2 and history of renal failure. By using stratified analysis, we evaluated whether the relationship

between hypouricemia and reduced GFR was modified by diabetic status, because serum uric acid is often low due to the effects of glycosuria on increasing uric acid excretion in diabetes [23].

All tests were two-tailed, and P<0.05 was considered statistically significant. Statistical analyses were performed with SPSS for Windows (Version 18.0; SPSS, Chicago, IL, USA), Stata / MP software (Version 12.1; Stata Corp, College Station, TX, USA), and EZR (Saitama Medical Center, Jichi Medical University), a graphical user interface for R (The R Foundation for Statistical Computing) [24].

Results

Of the 667,218 individuals who participated in the SHC in 2008, we excluded those for whom serum uric acid or serum creatinine levels were not measured. While these measurements are not mandatory items of the SHC, they are included in some regions. Those with missing covariates were also excluded, resulting in a final study population of 227,645 (Supplementary Figure 1). There were no major differences between included and excluded individuals with respect to serum uric acid levels and BMI, but the latter group was slightly younger and more likely to have a history of stroke, heart disease, or renal failure (Supplementary Table 1).

Among the 90,710 men and 136,935 women, 193 (0.2%) and 540 (0.4%) were identified as having hypouricemia, respectively. The prevalence of hypouricemia did not change significantly with age in men (*P* for trend = 0.24), but decreased with age in women (*P* for trend < 0.001) (Figure 1). Next, we investigated the association between serum uric acid levels and eGFR (Supplementary Figure 2). A higher proportion of men with hypouricemia had reduced eGFR (< 60 ml/min/1.73 m^2), whereas a higher proportion of women with hypouricemia had an eGFR $\geq$ 90 ml/min/1.73 m^2, compared with men and women with serum uric acid levels of 4.1 to 5.0 mg/dL.

Men with hypouricemia had a higher BMI compared with those in the reference category (i.e., serum uric acid levels of 4.1 to 5.0 mg/dL) (Table 1). In contrast, women with hypouricemia had a lower BMI, a lower prevalence of hypercholesterolemia, lower low-density lipoprotein cholesterol levels, higher high-density lipoprotein cholesterol levels, lower triglyceride levels, lower alanine transaminase levels, lower gamma-glutamyl transpeptidase levels, and a higher eGFR, compared with those in the reference category (Table 2). In both men and women, there were no differences between those with hypouricemia and those in the reference category with regard to past history of stroke, heart disease, or renal failure.

Men with hypouricemia had an unadjusted odds ratio (OR) of 1.71 (95% confidence interval [CI], 1.16 - 2.53) for reduced eGFR compared with those in the reference category (Supplementary Table 2). The association did not change after adjusting for potential risk factors of reduced eGFR (i.e., age, smoking, drinking, hypertension, diabetes mellitus, and hypercholesterolemia) (OR, 1.86; 95% CI, 1.25 - 2.78). The association was only partially attenuated after additionally adjusting for obesity (OR, 1.85; 95% CI, 1.24 - 2.76) and history of renal failure (OR, 1.83; 95% CI, 1.23 - 2.74).

Women with hypouricemia had an unadjusted OR of 0.60 (95% CI, 0.42-0.85) for reduced eGFR compared with those in the reference category. The direction and magnitude of the association did not change after adjusting for potential risk factors of reduced eGFR (OR, 0.61; 95% CI, 0.43 - 0.88). Moreover, the association did not change after additionally adjusting for obesity (OR, 0.61; 95% CI, 0.43 - 0.87) and history of renal failure (OR, 0.61; 95% CI, 0.43 - 0.86).

Subgroup analyses stratified by diabetic status were performed, because diabetes mellitus is reportedly associated with both hypouricemia and hyperuricemia [23]. Point estimates of the OR of hypouricemia were similar in those with and without diabetes compared with the entire study population (men without diabetes; 1.81, 95% CI, 1.17-2.80; men with diabetes; 1.88, 95% CI, 0.68-5.20; women without diabetes; 0.62, 95% CI, 0.43-0.89; women with diabetes; 0.49, 95% CI, 0.12-

2.05), although the association was not significant in participants with diabetes due to the small sample size (Figure 2).

Discussion

In this study, the prevalence of hypouricemia and its association with reduced eGFR was examined using nationwide data in Japan, leading to two new insights. First, the prevalence of hypouricemia decreased with age in women, but not in men. Second, hypouricemia was associated with reduced eGFR in men, but not in women. These findings suggest the possibility that men with hypouricemia are at higher risk of reduced kidney function.

The present study found that the prevalence of hypouricemia in the general population was 0.2% in men and 0.4% in women, respectively. This prevalence is consistent with that reported in previous reports, i.e., 0.15% (5/3,258) in outpatients [25], 0.34% in 586 normal subjects [2], and 0.23% (4/1,730) in Japanese children aged 9 to 15 years [26]. Our study, however, is the first to report a gender difference, demonstrating that the prevalence remains constant at any age in men, whereas it decreases with age in women. Although the reason for this is unclear, a possible role of estrogen has been suggested, given that serum uric acid levels increase after menopause [27-29]. Because 80% of Japanese women undergo menopause between the ages 45 and 54 years [30], menopausal status may explain the decrease in prevalence of hypouricemia with age in women. Unfortunately, information regarding menopausal status was not available in this study.

Another important and interesting finding was the association of hypouricemia with reduced eGFR in men, but not in women. To our knowledge, this study is the first to show a moderately J-shaped association between serum uric acid levels and the prevalence of reduced eGFR in men. That is, both hypouricemia and hyperuricemia are associated with an increased risk of reduced eGFR in men.

Many observational studies have reported that increased serum uric acid levels independently predict the development of reduced eGFR in the general population [31-36]. However, very few studies have assessed the association between hypouricemia and the risk of reduced eGFR. One possible reason for this is that the lower cutoff level for serum uric acid was higher than 2.0 mg/dL. In the present study, hypouricemia was associated with reduced eGFR in men, but not among participants with serum uric acid levels of 2.1 to 3.0 mg/dL or 3.1 to 4.0 mg/dL, compared with those in the reference category. Thus, categorization with higher cutoff levels may cancel out the effects on reduced eGFR. Another reason might be related to the small sample size, i.e., the statistical power of previous studies was insufficient to detect the influence of hypouricemia. A retrospective cohort study conducted in Taiwan showed a moderately J-shaped effect of serum uric acid on the incidence of chronic kidney disease, which was defined as a decrease of GFR to less than 60 mL/min/1.73 m^2 at a follow-up examination. Moreover, that study showed significantly increased hazard ratios in participants with hyperuricemia and moderately increased hazard ratios in participants with hypouricemia, although the latter estimates were not significant [37].

Given that uric acid is considered one of the most important antioxidants in human plasma [3-5], it is tempting to speculate that hypouricemia, through decreased antioxidant potential, increases the risk of reduced kidney function. Low uric acid levels have been linked to several inflammatory and degenerative diseases, such as acute graft-versus-host disease [42] and neurological diseases, such as Alzheimer's disease, Huntington's disease, Parkinson's disease, and multiple sclerosis[43]. These associations have been attributed to the reduced antioxidative capacity associated with hypourisemia [42,43].

Another possibility is that the control of renal uric acid, rather than serum uric acid levels *per se*, is associated with reduced kidney function. A previous study using two community-based general population samples found that subjects having the common nonsense mutation, W258X, which is

responsible for renal hypouricemia, showed significantly reduced renal function independently of age, sex, BMI, hypertension, and serum uric acid levels [8]. Furthermore, a recent study using the statistical genetics approach of Mendelian randomization demonstrated that increased genetic risk score, which was strongly associated with serum uric acid levels, was associated with significantly improved renal function in men, but not in women [44]. Analysis of individual genetic variants demonstrated that the effect size associated with serum urate did not correlate with that associated with renal function in the Mendelian randomization model [44]. This is consistent with the possibility that the physiological action of these genetic variants in raising serum urate correlates directly with improved renal function [44]. Taken together, genetic variants which reduce or increase serum uric acid levels, rather than serum uric acid *per se*, may be associated with kidney function.

A recent study using the statistical genetics approach of Mendelian randomization has provided new insights regarding uric acid. In contrast to previous observational findings, there is no strong evidence for causal associations between uric acid and ischaemic heart disease or blood pressure [45]. The approach has also demonstrated that elevated serum uric acid is a consequence, rather than a cause, of adiposity [46,47], and is not a cause of type 2 diabetes [48] or metabolic syndrome [49]. Although we could not rely on Mendelian randomization due to the lack of genetic data, these reports and our results suggest that the association between uric acid levels and reduced kidney function is far more complex than previously thought.

From a clinical perspective, our results suggest that the presence of hypouricemia should prompt clinicians to look for the presence of reduced kidney function in men. Although direct evidence is lacking, reduced eGFR may be associated with AKI or nephrolithiasis, given that they are both risk factors for reduced eGFR [12, 13] and are well-known complications in patients with renal hypouricemia [9-11]. The gender specificity of the association between hypouricemia and reduced eGFR in men might be explained by the fact that the majority of patients with exercise-induced AKI

associated with renal hypouricemia are men, with a male:female ratio of 8:1 [10]. Although the short-term prognosis of exercise-induced AKI associated with renal hypouricemia is generally good [10], further clinical studies are needed to determine the long-term prognosis of patients with hypouricemia.

Study Limitations and Strengths

The present study has several limitations. First, there may have been selection bias in the study population, because all participants underwent annual health checkups and may thus be generally healthier than those who did not. However, the prevalence of hypouricemia in our study was in line with previous studies that targeted the general population. Second, we cannot rule out the possibility of a confounding effect by other factors which cause hypouricemia, such as malignancies, severe liver disease, medication use, and dietary factors. Hypouricemia can be caused not only by enhanced uric acid excretion, but also by decreased uric acid production or uric acid oxidation due to treatment with uricase. Moreover, hypouricemia in some participants might not be attributed to renal hypouricemia, as information on the primary cause of hypouricemia was not available. However, levels of aspartate transaminase, alanine transaminase, and gamma-glutamyl transpeptidase in this study were not indicative of severe liver diseases. Unfortunately, detailed information on medication use was not available. However, medication treatment for hyperuricemia rarely results in a serum uric acid level ≤ 2 mg/dL. This study was conducted using data collected in 2008, when febuxostat, a non-purine selective xanthine oxidase inhibitor, was unavailable in Japan. Dietary information was also unavailable. While dietary factors can affect serum uric acid levels, even vegetarians and individuals who eat fish but not meat rarely had serum uric acid levels ≤ 2 mg/dL [46]. Thus, it is unlikely that this would have affected our main results. Third, despite adjusting for potential confounding factors, residual confounding remains possible. Finally, given the cross-sectional design of this study, causality could not be determined. However, it is unlikely that reduced eGFR causes hypouricemia.

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One strength of this study was its large sample population. This study was a large-scale cross-sectional study with participants from all over Japan, and included more than 700 individuals with hypouricemia. To the best of our best knowledge, this is the first study to demonstrate the prevalence of hypouricemia stratified by age and gender and assess the association between hypouricemia and reduced eGFR.

In conclusion, we found that hypouricemia is associated with reduced eGFR in men. Further studies will be needed to clarify the true biological and clinical significance of hypouricemia.

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Figure legends

Figure 1. Prevalence of hypouricemia by gender and age.

Trends were significant for women (□; *P*<0.001), but not for men (■; *P*=0.24).

Figure 2. Forest plot showing odds ratios with 95% confidence intervals for the relationship between serum uric acid levels and reduced kidney function.

All analyses were adjusted for the following covariates: age (per 10-year increase), daily drinker, current smoker, hypertension, hypercholesterolemia, obesity, and history of renal failure.