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Original Investigation

Development of Nephrolithiasis in Asymptomatic Hyperuricemia: A Cohort Study

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Background: Although the association between gout and nephrolithiasis is well known, the relationship between asymptomatic hyperuricemia and the development of nephrolithiasis is largely unknown.

Study Design: Cohort study.

Setting & Participants: 239,331 Korean adults who underwent a health checkup examination during January 2002 to December 2014 and were followed up annually or biennially through December 2014.

Predictor: Baseline serum uric acid levels of participants.

Outcome: The development of nephrolithiasis during follow-up.

Measurements: Nephrolithiasis is determined based on ultrasonographic findings. A parametric Cox model was used to estimate the adjusted HRs of nephrolithiasis according to serum uric acid level.

Results: During 1,184,653.8 person-years of follow-up, 18,777 participants developed nephrolithiasis (incidence rate, 1.6/100 person-years). Elevated uric acid level was significantly associated with increased risk for nephrolithiasis in a dose-response manner (P for trend < 0.001) in men. This dose-response association was not observed in women. In male participants, multivariable-adjusted HRs for incident nephrolithiasis comparing uric acid levels of 6.0 to 6.9, 7.0 to 7.9, 8.0 to 8.9, 9.0 to 9.9, and ≥10.0 mg/dL with uric acid levels < 6.0 mg/dL were 1.06 (95% CI, 1.02-1.11), 1.11 (95% CI, 1.05-1.16), 1.21 (95% CI, 1.13-1.29), 1.31 (95% CI, 1.17-1.46), and 1.72 (95% CI, 1.44-2.06), respectively. This association was observed in all clinically relevant subgroups and persisted even after adjustment for homeostasis model assessment of insulin resistance and high-sensitivity C-reactive protein level.

Limitations: Dietary information and computed tomographic diagnosis of nephrolithiasis were unavailable.

Conclusions: In this large cohort study, increased serum uric acid level was modestly and independently associated with increased risk for the development of nephrolithiasis in a dose-response manner in apparently healthy men.

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INDEX WORDS: Nephrolithiasis; uric acid; hyperuricemia; cohort study; risk factor; urinary stones; kidney stone; abdominal ultrasound; sex differences; Korea.

The prevalence of nephrolithiasis in the United States has doubled during the past 3 decades, causing significant health and economic burdens.[1] Such a trend in prevalence has also been observed in most European countries and Southeast Asia.[2] Once diagnosed, nephrolithiasis can recur, with a relapse rate of 50% in 5 to 10 years and 75% in 20 years.[3] Although approximately one-third of patients are asymptomatic, most patients present symptomatically with renal colic, infection, renal tract obstruction requiring surgical intervention, and kidney failure.[4] Nephrolithiasis is a multifactorial disease influenced by age, sex, ethnicity, and geography.[1] Nephrolithiasis has been increasingly recognized as a systemic disorder, and there is growing emphasis on modifiable risk factors such as obesity, diabetes, hypertension, and metabolic syndrome.[1,5-7]

Hyperuricemia, an important mediator of gout, has increased in recent decades, possibly due to the increasing prevalence of obesity, medications, and lifestyle changes, such as increased consumption of sugar-sweetened beverages, purine-rich foods, and alcohol.[8,9] Patients with gout frequently present with multiple comorbid conditions, such as hypertension, chronic kidney disease (CKD), obesity, diabetes, dyslipidemia, and cardiovascular disease.[10] Interestingly, recent studies have suggested that elevated

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serum uric acid levels, even in the asymptomatic population without gout, are associated with risk for nonalcoholic fatty liver disease, diabetes, hypertension, coronary heart disease, and CKD.[9,11] As well as other comorbid conditions, the association between gout and nephrolithiasis has long been recognized.[12] However, it is unclear whether hyperuricemia itself affects the development of nephrolithiasis. To our knowledge, no previous longitudinal studies have evaluated the association between uric acid level and the occurrence of nephrolithiasis in the general population without gout. Therefore, we evaluated the association between hyperuricemia with the development of nephrolithiasis in a large cohort of Korean adults free from gout and nephrolithiasis at baseline who participated in a health screening examination program.

METHODS

Study Population

This study was part of The Kangbuk Samsung Health Study, which is a cohort study of Korean men and women 18 years or older who underwent a comprehensive annual or biennial examination from January 2002 through December 2014 at Kangbuk Samsung Hospital Total Healthcare Centers in Seoul or Suwon, South Korea. More than 80% of participants were employees of various companies or local governmental organizations and their spouses. In South Korea, the Industrial Safety and Health Law requires annual or biennial health screening examinations of all employees without charge. Other participants voluntarily underwent screening examinations at the health examination center. The present analysis included all study participants who had at least one follow-up visit through December 31, 2014 (n = 263,243).

Of these participants, 23,912 were excluded as follows: 7,735 had missing uric acid, body mass index (BMI), homeostasis model assessment of insulin resistance (HOMA-IR), high-sensitivity C-reactive protein (hs-CRP), or abdominal ultrasonography data; 759 participants had polycystic kidney disease, a deformity, hypoplasia, dysgenesis, renal tumor, renal cancer, or a kidney transplant or were postsurgical on the initial sonographic examination; 4,230 participants had glomerular filtration rates (GFRs) < 60 mL/min/1.73 m^2 at baseline; 656 had a history of gout or were taking medication for gout; and 11,683 participants had a history of urinary stones, were taking a prescription for urinary stones, or had nephrolithiasis on ultrasonography of the abdomen at baseline. Because some participants met more than one of the exclusion criteria, the total number of participants eligible for this study was 239,331. The study was approved by the Institutional Review Board of Kangbuk Samsung Hospital, which waived the requirement for informed consent due to the use of deidentified data obtained as part of routine health screening examinations (2016-10-036).

Measurement

All participants were examined at Kangbuk Samsung Hospital Health Screening Center clinics in Seoul or Suwon. Data for demographic characteristics, smoking status, alcohol consumption, physical activity, educational level, and medical history of hypertension, diabetes, and kidney disease, including kidney stone and medication use, were collected by standardized self-administered questionnaires, as previously described.[13,14] Smoking status was subdivided into never, former, and current smokers. Alcohol consumption was subdivided into ≤20 and >20 g/d. The weekly frequency of moderate- or vigorous-intensity physical activity was assessed and categorized into at least 3 times per week of moderate to vigorous intensity aerobic activity versus fewer than 3 times per week.

All physical characteristics, including sitting blood pressure, weight, and height, were measured by trained nurses. Sitting blood pressure was measured by standard mercury sphygmomanometers. Weight was measured in light clothing without shoes to the nearest 0.1 kg using a bioimpedance analyzer (InBody 3.0 and Inbody 720; Biospace Co) validated for reproducibility and accuracy of body composition measurements[15] and calibrated every morning before testing started. Height was measured to the nearest 0.1 cm using a stadiometer with the participant standing barefoot. BMI was calculated as weight in kilograms divided by height in meters squared and was classified according to Asian-specific criteria[16]: underweight, BMI < 18.5 kg/m^2; normal weight, BMI of 18.5 to <23 kg/m^2; overweight, BMI of 23 to <25 kg/m^2; and obese, BMI ≥25 kg/m^2.

Blood specimens were collected from the antecubital vein after at least a 10-hour fast. Blood tests included total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, fasting glucose, uric acid, hs-CRP, and creatinine. During the study period, serum creatinine was measured using the kinetic alkaline picrate (Jaffé) method in an automated chemistry analyzer (from 2002-2009, Advia 1650 Autoanalyzer, Bayer Diagnostics; from 2010-2013, Modular D2400, Roche). We calculated estimated GFR using the CKD-EPI (CKD Epidemiology Collaboration) creatinine equation. Because the laboratory method used to determine serum creatinine level did not involve use of an isotope-dilution mass spectrometry (IDMS) method from 2002 to 2009, we reduced creatinine levels by 5%, the calibration factor used to adjust nonstandardized MDRD (Modification of Diet in Renal Disease) Study samples to IDMS.[17,18] The HOMA-IR, an index used to quantify β-cell function and insulin resistance, was calculated by multiplying fasting insulin (mg/dL) by fasting glucose (mg/dL) and then dividing by a correction factor of 405.[19]

Nephrolithiasis was assessed on routine ultrasonographic examination instead of based on the presence of renal colic or the passage of stones. Ultrasonography of the abdomen was performed routinely in all participants at baseline and at each visit. Experienced radiologists who were unaware of the aim of the study performed ultrasonography of the abdomen using a Logic Q700 MR 3.5-MHz transducer (GE). Images were captured in a standard manner with participants in the supine position with the right arm raised above the head. Hyperechoic structures causing acoustic shadowing that were seen in the collecting system on ultrasonography were diagnosed as renal stones.[20]

Statistical Analyses

Participants were divided into 6 groups according to serum uric acid level: <6.0, 6.0 to 6.9, 7.0 to 7.9, 8.0 to 8.9, 9.0 to 9.9, or ≥10.0 mg/dL in men and <4.0, 4.0 to 4.9, 5.0 to 5.9, 6.0 to 6.9, 7.0 to 7.9, or ≥8.0 mg/dL in women. All data were presented as mean ± standard deviation, median with interquartile range (IQR), or number and percentage. Characteristics of study participants were explored according to uric acid level. To compare among different serum uric acid levels, 1-way analysis of variance was used for continuous variables, and χ^2 test was used for categorical variables. There is no universally accepted definition of hyperuricemia based solely on uric acid level. To define hyperuricemia, serum uric acid concentration cutoffs of >7.0 mg/dL for men and >6.0 mg/dL for women are commonly used in clinical laboratories. These cutoffs have been proposed in previously published studies in relation to cardiovascular disease outcomes to define hyperuricemia.[21] Also, serum uric acid level < 6.0 mg/dL is considered normal for preventing uric acid crystal deposition.[22]