

## Association of Metabolic Syndrome Traits and Severity of Kidney Stones: Results From a Nationwide Survey on Urolithiasis in Japan

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**Background:** Although metabolic syndrome and its individual components have been associated with kidney stone disease, whether the clustering of metabolic syndrome traits increases the severity of kidney stone disease has not been examined in a large-scale study.

**Study Design:** Cross-sectional analysis.

**Setting & Participants:** Data were obtained from 30,448 patients enrolled in the 6th Nationwide Survey on Urolithiasis in Japan conducted in 2005. Patients with lower urinary tract stones, struvite stones, cystine stones, or hyperparathyroidism and those younger than 15 years were excluded.

**Predictor:** Number of metabolic syndrome traits (obesity [body mass index  $\geq 25$  kg/m<sup>2</sup>], diabetes, hypertension, and dyslipidemia).

**Outcomes:** Severe form of kidney stone disease, defined as recurrent and/or multiple stones, and abnormalities in urine constituents (hypercalciuria, hyperuricosuria, hyperoxaluria, and hypocitraturia).

**Results:** 11,555 patients were included in the final analyses. Proportions of patients with recurrent and/or multiple stones were 57.7%, 61.7%, 65.2%, 69.3%, and 73.3% with 0, 1, 2, 3, and 4 metabolic syndrome traits, respectively ( $P < 0.001$ ). There was a significant and stepwise increase in the odds of recurrent and/or multiple stones after adjustment for age and sex. In patients with 4 metabolic syndrome traits, the odds was 1.8-fold greater compared with patients with 0 traits (OR, 1.78; 95% CI, 1.22-2.66). In addition, the presence of metabolic syndrome traits was associated with significantly increased odds of having hypercalciuria, hyperuricosuria, hyperoxaluria, and hypocitraturia after adjustment for age and sex.

**Limitations:** Cross-sectional design, absence of dietary data, ill-defined diagnostic criteria for metabolic syndrome traits, and missing data for the majority of participants.

**Conclusions:** Metabolic syndrome trait clustering is associated with greater severity of kidney stone disease; increased urinary calcium, uric acid, and oxalate excretion; and decreased urinary citrate excretion. These results suggest that kidney stone disease should be regarded as a systemic disorder linked to metabolic syndrome.

*Am J Kidney Dis.* 61(6):923-929. © 2013 by the National Kidney Foundation, Inc.

**INDEX WORDS:** Nephrolithiasis; metabolic syndrome X; obesity.

The annual incidence of upper urinary tract stones in Japan has increased almost 3-fold from 43.7 per 100,000 (63.8 for men and 24.3 for women) in 1965 to 134 per 100,000 (192 for men and 79.3 for women) in 2005.<sup>1</sup> Although this trend might be attributable in part to advances in diagnostic imaging, increased diagnosis of asymptomatic stones by medical checkup, and an aging population, westernized eating habits and lifestyle changes in the Japanese population have been proposed as the main reasons for this increase, suggesting that kidney stone disease is a form of lifestyle-related disease. Recent epidemiologic studies have shown an increased prevalence of kidney stones in patients with lifestyle-related diseases, such as obesity,<sup>2</sup> type 2 diabetes,<sup>3</sup> and hypertension.<sup>4,5</sup> Collectively, these medical conditions are now known as metabolic syndrome, which has received a great deal of attention in recent years as a risk factor for cardiovascular disease development.<sup>6</sup>

Although metabolic syndrome also has been associated with kidney stone disease,<sup>7-9</sup> whether the clustering of metabolic syndrome traits increases the severity of kidney stone disease has not been examined in a large-scale study. We therefore investigated the association of number of metabolic syndrome traits with severity of kidney stone disease, assessed by the number of existing stones and number of stone episodes, as well as abnormalities in urine constituents,

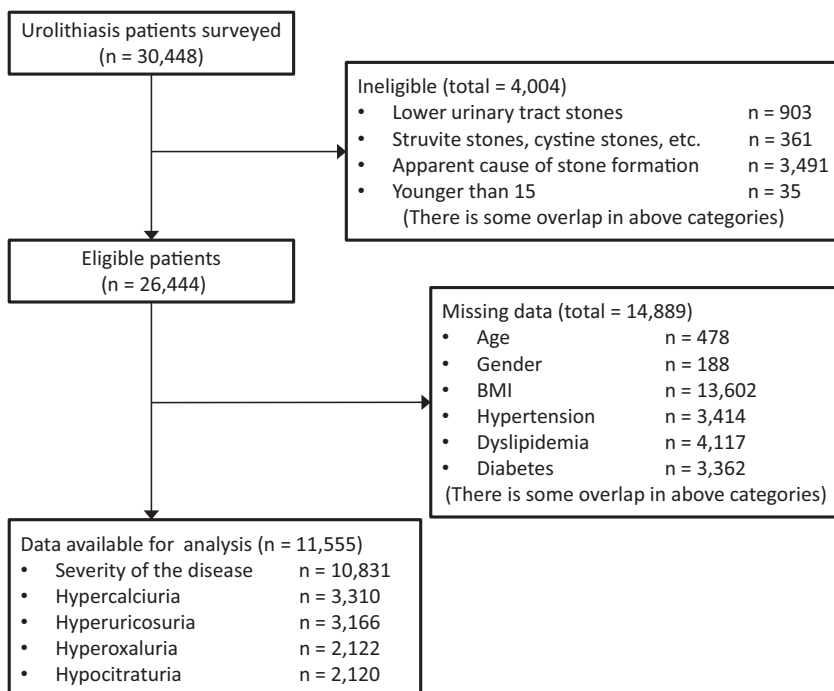
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Received July 21, 2012. Accepted in revised form December 27, 2012. Originally published online February 21, 2013.

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0272-6386/\$36.00

<http://dx.doi.org/10.1053/j.ajkd.2012.12.028>



**Figure 1.** Flow diagram of the study cohort. Abbreviation: BMI, body mass index.

using a nationally representative sample of Japanese patients with kidney stones.

## METHODS

### Study Population

We retrospectively analyzed detailed clinical data from 30,448 patients with urolithiasis enrolled in the 6th Nationwide Survey on Urolithiasis in Japan conducted in 2005.<sup>1</sup> This survey was designed to estimate the annual incidence of urolithiasis and included all 1,218 hospitals approved by the Japanese Board of Urology, thus covering nearly all urologists practicing in Japan. Materials and methods used in the surveys have been described previously.<sup>1</sup> In brief, the enrolled hospitals were asked by way of a mailed questionnaire to investigate all patient visits in 2005 that resulted in a diagnosis of urolithiasis. Patients with only a history of stone passage (patients with no stones in 2005) were excluded from the study. The survey included questions about the age and sex of patients with stones, stone location (upper or lower urinary tract or both), and number of stone episodes (first time or recurrent). The survey also included a detailed questionnaire about individual patient characteristics, such as body size (height and weight), number of stones (single or multiple), possible causes of stone formation (urinary obstruction, urinary tract infection, prolonged immobility, primary hyperparathyroidism, renal tubular acidosis, cystinuria, hypercalciuria, hyperuricemia, and medication), abnormalities in urine chemistry (hypercalciuria, hyperuricosuria, hyperoxaluria, and hypocitraturia), stone composition (calcium oxalate, calcium phosphate, uric acid, magnesium ammonium phosphate, cystine, and others), and comorbid conditions (diabetes, hypertension, dyslipidemia, and osteoporosis). The response to individual questionnaires was obtained from 174 hospitals, including detailed clinical data for 30,448 patients with urolithiasis.

Because previous reports have suggested that metabolic syndrome might be associated with kidney stones composed of calcium oxalate or uric acid, we excluded patients with only lower urinary tract stones; with struvite stones, cystine stones, and other types of rare stone composition; who had a clinically apparent

cause of stone formation (urinary obstruction, urinary tract infection, prolonged immobility, primary hyperparathyroidism, renal tubular acidosis, cystinuria, and medication); and younger than 15 years. The number of patients who were excluded based on these criteria was 4,004. We also excluded another 14,889 patients with missing data for age, sex, body size, diabetes, hypertension, and dyslipidemia. A total of 11,555 patients was included in the final analyses (Fig 1).

### Exposures

The number of metabolic syndrome traits (obesity, hypertension, dyslipidemia, and diabetes) was counted for each patient. Obesity was defined as body mass index (BMI)  $\geq 25$  kg/m<sup>2</sup>. Although diagnostic criteria for other traits were not defined in the survey, commonly used criteria in Japan were as follows: hypertension, blood pressure  $\geq 140/90$  mm Hg; dyslipidemia, low-density lipoprotein cholesterol level  $\geq 140$  mg/dL, high-density lipoprotein cholesterol level  $< 40$  mg/dL, or triglyceride level  $\geq 150$  mg/dL; diabetes, fasting plasma glucose level  $\geq 126$  mg/dL, 2-hour plasma glucose level by 75-g glucose tolerance test  $\geq 200$  mg/dL, or hemoglobin A<sub>1c</sub> level  $\geq 6.5\%$ .

### Outcomes

Severe kidney stone disease was defined as recurrent and/or multiple stones. Numbers of stone episodes (first time/recurrent) and existing stones (single/multiple) were reported based on medical and radiology records. Abnormalities in urine constituents (hypercalciuria, hyperuricosuria, hyperoxaluria, and hypocitraturia) were reported based on the medical record. Commonly used criteria in Japan were as follows: (1) hypercalciuria, urinary calcium excretion  $\geq 4.0$  mg/kg/d; (2) hyperoxaluria, urinary oxalate excretion  $\geq 45$  mg/d; (3) hyperuricosuria, urinary uric acid excretion  $\geq 800$  mg/d in men and  $\geq 750$  mg/d in women; and (4) hypocitraturia, urinary citrate excretion  $< 320$  mg/d.

### Analytical Procedures

The severity of kidney stone disease, assessed by the number of existing stones and number of stone episodes, and abnormalities in

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