Nephrolithiasis and Increased Blood Pressure Among Females With High Body Mass Index

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- **Background:** We hypothesized that one reason for the heterogeneity in previously reported links between kidney stones and blood pressure (BP) was the differential effects of nephrolithiasis among subgroups of individuals. In particular, we hypothesized that the association between stone history and BP may vary with respect to sex and body size.

- **Methods:** Data from the Third National Health and Nutrition Examination Survey were used to estimate the association between history of stone disease and odds of prior diagnosis of hypertension and mean difference in systolic BP, diastolic BP, and pulse pressure. Nine hundred nineteen persons with a history of stones and 19,120 persons without stones were available for analysis.

- **Results:** In women, it was estimated that stone formers (SFs) experienced a 69% increase in odds of self-reported hypertension (95% confidence interval [CI], 1.33 to 2.17; \( P < 0.001 \)). No significant difference was found in men. The estimated difference in mean systolic and diastolic BP comparing SFs with non-SFs increased with body mass index in both sexes, but was more pronounced in women. Mean systolic BPs in women SFs in quintiles 4 and 5 of body mass index were 7.62 mm Hg (95% CI, 1.04 to 14.2; \( P = 0.024 \)) and 4.36 mm Hg (95% CI, 0.30 to 8.42; \( P = 0.036 \)) greater than those in similar women non-SFs, respectively.

- **Conclusion:** Our findings not only support the link between kidney stone disease and BP, but also suggest that overweight women SFs may be at significantly increased risk for hypertension. *Am J Kidney Dis* 46:263-269.

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Several epidemiological studies have suggested an association between nephrolithiasis and hypertension. Madore et al considered data from a cohort of women aged 34 to 59 years and found a significant cross-sectional relationship between stone history and prior diagnosis of hypertension, as well as a positive association between stone history and incident hypertension. In a follow-up study, Madore et al found similar associations in a cohort of men aged 40 to 75 years, although the magnitude of this relationship was not as great as that found in the Nurses’ Health Study.

Recently, Borghi et al investigated the pathogenic link between hypertension and stone disease. After adjustment for body mass index (BMI), they found that several urinary stone risk factors, including oxaluria, calcium, and supersaturation of calcium oxalate, were significantly greater in hypertensive subjects compared with age- and sex-matched subjects without hypertension. They also found that the risk for stone formation in patients prospectively followed up over time was significantly greater in hypertensive subjects.

Multiple studies found hypertension to be a major risk factor for cardiovascular disease (CVD)–related morbidity and mortality. Currently, the prevalence of hypertension is estimated to be 28% in North America. Despite much research aimed at identifying risk factors for hypertension, manifestations of high blood pressure (BP) often are unclear. Additional work is needed to identify patient subgroups that may be at increased risk for hypertension. Given the increasing prevalence of renal stones in the US population, if a true association between stone formation and hypertension exists, this would represent a large at-risk population.

The reported magnitude of the relationship between stones and BP has varied greatly from study to study. We hypothesized that one reason for this heterogeneity is the existence of subgroups at particular risk for increased BP in the presence of nephrolithiasis. Specifically, we hypothesized that the association between stones and BP may vary with respect to sex and body size and sought to test this hypothesis by using...
data from the Third National Health and Nutrition Examination Survey (NHANES III).

METHODS

Study Population

NHANES III was conducted between 1988 and 1994, representing one of several surveys performed by the National Center for Health Statistics. A detailed description of the methods used in the survey is available elsewhere. Briefly, the survey was designed to provide national estimates of health and nutritional status in the civilian noninstitutionalized US population aged 2 months and older. Data collected in NHANES III included, but were not limited to, sociodemographic factors, medical history, and medication use. Although subsequent surveys have been conducted by the National Center for Health Statistics, NHANES III is the most recent to include questions regarding nephrolithiasis. A total of 33,994 persons were interviewed for NHANES III. In this study, we restrict our attention to survey participants aged 17 to 90 years with information on the lifetime occurrence of kidney stones (N = 20,029).

Exposure and Outcome Definitions

The primary exposure in our analysis is any history of nephrolithiasis. All participants who answered “yes” to the question “Have you ever had a kidney stone?” (n = 919) were considered to have a history of nephrolithiasis. Persons who responded “don’t know” (n = 13) or who did not respond (n = 8) were excluded.

We considered 4 BP outcomes: self-reported previous diagnosis of hypertension, systolic BP (SBP), diastolic BP (DBP), and pulse pressure calculated as the difference between SBP and DBP. As part of the NHANES survey, participants were asked “Have you ever been told by a doctor or other health professional that you had hypertension, also called high blood pressure?” Persons answering “yes” to this question were considered to have a history of hypertension. SBP and DBP, averaged over 1 to 6 repeated measurements, also were considered. A total of 19,120 NHANES participants had at least 1 recorded BP measurement. Of these, more than 99% had 3 to 6 measurements available. A certified operator performed BP measurements using a mercury sphygmomanometer and a standardized procedure during the home interview and physical examination portions of the survey. A cuff size appropriate for the participant’s arm circumference was used. Quality control was ensured by operator recertification, procedural checklists, and data review.

Statistical Analysis

All point estimates and SEs incorporate NHANES III survey weights, which account for unequal probability of selection into the NHANES sample and survey nonresponse. Variance estimates were computed by means of the linearization method. Age-adjusted comparisons of patient characteristics by history of nephrolithiasis were performed by using linear regression for continuous covariates and logistic regression for binary characteristics.

It was hypothesized a priori that the relationship between stone history and hypertension may differ with respect to sex and/or body size. As such, multiplicative interactions between stone history, sex, and BMI were formally tested, and stratum-specific point estimates for the association of interest are reported.

Logistic regression was used to estimate the association between stone history and self-reported prior diagnosis of hypertension. Covariates a priori identified as potential confounders in the relationship between BP and stone history were adjusted for. These included age, sex, race (African American versus other), BMI, history of CVD (myocardial infarction, stroke, congestive heart failure), diabetes, and smoking status (ever versus never). Other covariates considered as adjustment variables included dietary intake, insurance status, alcohol use, household income, and marital status. Components of dietary intake (milligrams per day of calcium, sodium, magnesium, and potassium) were estimated through a 24-hour recall survey administered during NHANES III data collection.

SBP, DBP, and pulse pressure were regressed on history of stone disease with adjustment for potential confounding factors listed by using multiple linear regression. Analyses were stratified by sex. Multiplicative interaction terms between stone history and BMI (modeled as both a continuous variable and categorized into quintiles) were formally tested, and stratum-specific point estimates and confidence intervals (CIs) were calculated. Regression diagnostics were used to determine outlying observations; however, no subject in the presented analysis was removed because of influence.

All statistical analyses were performed using conventional commercial software (Stata Statistical Software, release 8.0, 2003; Stata Corp, College Station, TX).

RESULTS

Age-adjusted patient characteristics extrapolated to the US noninstitutionalized population are listed in Table 1. Patients with a history of renal stones tended to be men and non–African American. Stone formers (SFs) were more likely to have smoked and had a greater prevalence of CVD. In univariate analyses, SFs were more likely to report a previous diagnosis of hypertension compared with non-SFs (32.7% versus 24.6%; P = 0.001), and both SBP and DBP were higher on average in SFs. Mean SBP was estimated to be 128.8 ± 0.8 mm Hg in SFs compared with 127.2 ± 0.3 mm Hg in non-SFs (P = 0.049). Similarly, mean DBP was estimated to be 77.4 ± 0.6 mm Hg in SFs compared with 75.7 ± 0.3 mm Hg in non-SFs (P = 0.023). No significant difference in pulse pressure was observed between SFs and non-SFs. Of SFs, approximately 39% were estimated to have received medication for their stones, 8% were estimated to have undergone extracorporeal shock-wave lithotripsy.
therapy, and 19% were estimated to have undergone surgery to remove a stone.

Prior Diagnosis of Hypertension

Model-based estimates of the association between history of nephrolithiasis and self-reported diagnosis of hypertension are listed in Table 2. After adjustment for age, race, smoking status, history of CVD, and diabetes, a marginally significant interaction between stone history and sex was found ($P = 0.056$). In women, it was estimated that SFs experienced a 69% increase in odds of reporting a prior diagnosis of hypertension (95% CI, 1.33 to 2.17; $P < 0.001$). In men, odds of reporting a previous hypertension diagnosis were 20% greater for SFs compared with non-SFs; however, this association was not statistically significant (95% CI, 0.88 to 1.64; $P = 0.237$). No additional interactions between stone history and age, race, or diabetes were observed. In addition, subanalyses of SFs did not show significant associations between stone treatment and self-reported hypertension.

### SBP, DBP, and Pulse Pressure

Figures 1 and 2 show estimates of mean differences in SBP and DBP comparing SFs with non-SFs. Given potential differences in the association between history of renal stones and self-reported hypertension, Table 2 provides adjusted odds ratios for hypertension diagnosis by history of kidney stones.

### Table 2. Population Characteristics by History of Stone Disease From NHANES III

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>History of Renal Stones (n = 919)</th>
<th>No History of Renal Stones (n = 19,110)</th>
<th>$P^*$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age at time of interview (y)</td>
<td>54.1 ± 0.7</td>
<td>43.1 ± 0.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Women (%)</td>
<td>40.4 ± 2.4</td>
<td>54.0 ± 0.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>African American (%)</td>
<td>3.8 ± 0.5</td>
<td>10.7 ± 0.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoking (ever v never)</td>
<td>60.3 ± 2.3</td>
<td>53.8 ± 0.8</td>
<td>0.007</td>
</tr>
<tr>
<td>CVD (%)</td>
<td>6.2 ± 0.8</td>
<td>4.0 ± 0.3</td>
<td>0.001</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>6.4 ± 1.0</td>
<td>5.0 ± 0.2</td>
<td>0.112</td>
</tr>
<tr>
<td>Mean BMI (kg/m²)</td>
<td>27.7 ± 0.3</td>
<td>26.6 ± 0.1</td>
<td>0.001</td>
</tr>
<tr>
<td>Calcium (mg/d)</td>
<td>816.1 ± 23.7</td>
<td>817.6 ± 9.9</td>
<td>0.951</td>
</tr>
<tr>
<td>Sodium (mg/d)</td>
<td>3,504.9 ± 92.7</td>
<td>3,414.3 ± 35.1</td>
<td>0.372</td>
</tr>
<tr>
<td>Potassium (mg/d)</td>
<td>2,950.7 ± 68.6</td>
<td>2,852.3 ± 22.5</td>
<td>0.184</td>
</tr>
<tr>
<td>Magnesium (mg/d)</td>
<td>307.3 ± 7.1</td>
<td>299.5 ± 2.5</td>
<td>0.322</td>
</tr>
<tr>
<td>Alcohol intake (g/d)</td>
<td>7.7 ± 1.3</td>
<td>9.5 ± 0.5</td>
<td>0.169</td>
</tr>
<tr>
<td>Mean SBP (mm Hg)</td>
<td>128.8 ± 0.8</td>
<td>127.2 ± 0.3</td>
<td>0.049</td>
</tr>
<tr>
<td>Mean DBP (mm Hg)</td>
<td>77.4 ± 0.6</td>
<td>75.7 ± 0.3</td>
<td>0.023</td>
</tr>
<tr>
<td>Pulse pressure (mm Hg)</td>
<td>51.4 ± 0.7</td>
<td>51.4 ± 0.3</td>
<td>0.977</td>
</tr>
<tr>
<td>Self-report of hypertension (%)</td>
<td>32.7 ± 2.3</td>
<td>24.6 ± 0.7</td>
<td>0.001</td>
</tr>
<tr>
<td>Treatment for stones (%)</td>
<td>Medication 39.4 ± 2.7</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Extracorporeal shock-wave lithotripsy</td>
<td>7.7 ± 1.5</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Surgery to remove stones (%)</td>
<td>18.9 ± 2.1</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

NOTE. Statistics expressed as mean or percentage ± SE and weighted to account for the stratified multistage sampling design of NHANES III. With the exception of age, all estimates are age adjusted and represent the estimated mean for a 50-year-old participant.

* $P$ are age adjusted and account for the stratified sampling design of NHANES III.

†CVD is defined as any history of myocardial infarction, stroke, or congestive heart failure.
The association between stone history and BP, presented results are stratified by sex ($P = 0.002$ and $0.005$ for SBP and DBP outcomes for the interaction between SF and sex, respectively). The association between BP (both SBP and DBP) and SFs also varied with BMI ($P = 0.002$ for SBP; $P = 0.065$ for DBP). Point estimates are presented for each BMI quintile. All estimates were adjusted for age, race, BMI, smoking status, history of CVD, and diabetes.

No differences in SBP or DBP were apparent comparing SFs with non-SFs in nonoverweight individuals. However, Figs 1 and 2 suggest an increasing trend in BP differences between SFs and non-SFs with respect to BMI. As shown in Fig 1, it was estimated that for women in BMI quintiles 4 and 5, history of nephrolithiasis was associated with 7.62–mm Hg (95% CI, 1.04 to 14.2; $P = 0.024$) and 4.36–mm Hg (95% CI, 0.30 to 8.42; $P = 0.036$) increases in SBP, respectively. As shown in Fig 2, it was estimated that women SFs in BMI quintiles 4 and 5 had DBPs 4.67 mm Hg (95% CI, 0.41 to 8.93; $P = 0.032$) and 2.92 mm Hg (95% CI, –0.60 to 6.43; $P = 0.102$) higher than those of similar women non-SFs. Although similar trends in BP differences between SFs and non-SFs were observed in men, the magnitude of these differences was smaller and not statistically significant. No significant difference in pulse pressure was observed, regardless of sex or BMI level (data not shown).

### DISCUSSION

We compared BP in persons with a history of nephrolithiasis with those without this history and found that the relationship varied with respect to sex and body size. After adjustment for potential confounders, we observed that a history of stone disease was associated with significantly increased odds of self-reported hypertension in...
women, but not men. In women in BMI quintiles 4 and 5, SFs had a significantly higher mean SBP and DBP. Conversely, no relationship between BP and stone history was observed in women at less than BMI quintile 4 (BMI < 27.3 kg/m²). Findings similar in nature, although of a smaller magnitude and not statistically significant, also were observed in male study participants. These observations substantiate the link between stone disease and hypertension previously reported in the literature and suggest that the variability in observed relationships between nephrolithiasis and BP reported may be caused by differential effects among subgroups of individuals.

The current analysis is consistent with previous studies suggesting a link between nephrolithiasis and BP. Borghi et al found that stone risk factors (calcium, oxalate, and calcium oxalate supersaturation) were greater in patients with than without hypertension (both men and women) and that the incidence of stone disease after a mean of approximately 7.6 years of follow-up was 14.3% (19 of 132 patients) in hypertensive patients compared with 2.9% (4 of 135 patients) in nonhypertensive patients (P = 0.001).

After adjustment for age, Madore et al found that a history of nephrolithiasis was associated with a 0.92–mm Hg (95% CI, 0.22 to 1.63) increase in mean systolic BP and a 0.70–mm Hg (95% CI, 0.25 to 1.15) increase in diastolic BP in a cohort of 89,376 female registered nurses in the United States. In addition, Madore et al found that after adjustment for age, BMI, and dietary calcium, sodium, potassium, magnesium, and alcohol intake, the odds of incident hypertension was 29% greater (CI, 1.12 to 1.41) in those with a history of nephrolithiasis when analyzing a cohort of 51,529 men. However, as in our study, no significant difference in mean SBP or DBP was observed in men.
The significant association between nephrolithiasis and hypertension that we found does not imply a causal relationship. Certainly, it is possible that 1 or more mechanisms associated with both stone disease and hypertension may be responsible for the development of both. Thus, the association between nephrolithiasis and hypertension could be attributable to many factors. First, increased BP may result from subclinical renal damage caused by multiple stone events. Patients with multiple stone episodes are at increased risk for urinary tract infections,11 undergo a variety of treatment regimens to remove stones, and may experience recurrent episodes of urinary tract obstruction. Experimental tubulointerstitial injury has been described as a mechanism for salt-sensitive hypertension.12 The synergistic effect of experiencing such recurrent renal insults, as SFs often do, may adversely affect BP.

The formation of calcium oxalate and brushite stones is associated with deposits of apatite particles in basement membranes of the thin loops of Henle and the deep medullary interstitium,13,14 although the extent of such plaque development and outcomes associated with it are still being investigated. Although interstitial inflammation and fibrosis and tubule cell injury and loss were not prominent, the particles achieve high densities in some regions, and this could ultimately affect BP. In addition, patients with brushite stones had extensive crystal formation in collecting ducts, associated with loss of tubular cells and interstitial scarring. Thus, the extent and location of renal injury may vary with stone type, leading to increased risk for hypertension.

Finally, calcium metabolism has a critical role in the pathogenesis of nephrolithiasis. Most stones are of the calcium oxalate type, and hypercalciuria is one of the most important risk factors for stone disease.15 In addition, calcium metabolism is a component in the pathogenesis of hypertension.16–18 Thus, it was suggested that hypercalciuria may be responsible for the association between stone disease and hypertension.16–18 In patients with interstitial calcium deposits described previously, the extent of deposits correlates directly with calcium levels in urine.19

The differential relationship between stone history and BP by sex is a significant finding that persists despite adjustment for key demographics and comorbidities associated with hypertension. There may be several reasons why the relationship between nephrolithiasis and BP is greater in women than men. Parks et al20 showed that women SFs tend to make more stones on average, undergo more treatments per stone episode, and experience more urinary tract infections compared with men SFs. In addition, women tend to form the less common struvite and calcium phosphate stones, which are associated with greater loss of renal function compared with other stone types.21–25 Because decreased renal function and BP are closely related, stone type may have a role in the link between nephrolithiasis and hypertension. We are not able to explore these links at present because stone type is not known for the patients described here.

We also observed that the association between stone history and BP varies with BMI. The difference in BP between SFs and non-SFs was greater in overweight persons (both women and men). To our knowledge, this significant interaction has not been reported in previous studies examining the relationship between stone disease and BP. However, hypertension has been notoriously linked to obesity and decreased renal function. In a previous report, we noted a link between stone formation and loss of renal function in subjects in the NHANES cohort, also seen in individuals with increased BMI.26

Our study has certain limitations. First, given the cross-sectional nature of the NHANES III survey, we cannot establish a temporal sequence of events and can only conclude that an association between stone history and hypertension exists. However, previous studies suggested a temporal sequence in the link between nephrolithiasis and BP,1,2 giving additional strength to the associations found in our study. We did not have information on the total number or type of stones for individuals. Although these data may have been helpful in further investigating the link between stone disease and BP, it was not necessary for establishing an association between stone history and BP. Next, it is unlikely that perfect classification of the exposure of interest was attained in the NHANES survey. With this said, the study is not likely to have recall bias because kidney stones are painful and rarely mistaken for any other disease. Finally, because this is an observational study, there is the potential for...
unmeasured confounders. However, we adjusted for the major demographic, dietary, and comorbid factors likely to have the largest impact on BP.

Our findings not only support the link between stone disease and BP, but also identify a key subgroup that may be differentially affected. We found that BP differences between SFs and non-SFs were greater in overweight individuals and that this effect was differential with respect to sex. These findings suggest that overweight women SFs represent a group of individuals that may be at significantly increased risk for hypertension and the associated morbidity and mortality. Although lower in magnitude, similar trends in the association between stones and hypertension were observed in men. Based on data from NHANES III, the prevalence of stone disease is estimated to be $4.1\% \pm 0.27\%$ in women and $6.3\% \pm 0.56\%$ in men, representing a large segment of the US population. Given the number of persons affected by stones, the public health impact of such a relationship between stone disease and BP could be substantial considering the costs and comorbidities associated with hypertension. As such, more focus on the early treatment and monitoring of SFs is recommended.

**REFERENCES**


