Family History and Risk of Kidney Stones

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Abstract. Kidney stones develop more frequently in individuals with a family history of kidney stones than in those without a family history; however, little information is available regarding whether the increased risk is attributable to genetic factors, environmental exposures, or some combination. In this report, the relation between family history and risk of kidney stone formation was studied in a cohort of 37,999 male participants in the Health Professionals Follow-up Study. Information on family history, kidney stone formation, and other exposures of interest, including dietary intake, was obtained by mailed questionnaires. A family history of kidney stones was much more common in men with a personal history of stones at baseline in 1986 than in those without a history of stones (age-adjusted prevalence odds ratio, 3.16; 95% confidence interval [CI], 2.90 to 3.45). During 8 yr of follow-up, 795 incident cases of stones were documented. After adjusting for a variety of risk factors, the relative risk of incident stone formation in men with a positive family history, compared with those without, was 2.57 (95% CI, 2.19 to 3.02). Family history did not modify the inverse association between dietary calcium intake and the risk of stone formation. These results suggest that a family history of kidney stones substantially increases the risk of stone formation. In addition, these data suggest that dietary calcium restriction may increase the risk of stone formation, even among individuals with a family history of kidney stones. (J Am Soc Nephrol 8: 1568–1573, 1997)

Kidney stones develop more frequently in individuals with a family history of kidney stones than in those without a family history; however, little information is available regarding whether the increased risk is attributable to genetic factors, environmental exposures or some combination. A positive family history of stones has been reported in 16% (1) to 37% (2) of patients who have formed a kidney stone, compared with 4% to 22% (1,3,4) in healthy control subjects. Proposed inherited traits predisposing to stone formation include hypercalciuria (5,6), defective oxalate transport (7), incomplete renal tubular acidosis (8), and increased uric acid production. Environmental exposures, such as diet, are thought to play an important role in stone formation (9); however, scant data exist on the potential interaction between family history of kidney stones and environmental influences.

To examine the influence of family history on kidney stone formation, we studied this relation in a cohort of 37,999 male participants in the Health Professionals Follow-up Study. We also examined the potential interaction between family history and dietary factors on risk of stone formation. In addition, we compared the results from 24-h urine collections in men with and without a family history of kidney stones.

Materials and Methods

Study Population

The Health Professionals Follow-up Study is a longitudinal study of diet and disease among 51,529 male dentists, optometrists, osteopaths, pharmacists, podiatrists, and veterinarians who were 40 to 75 yr of age in 1986. The participants returned a mailed questionnaire in 1986 concerning diet, medical history, and medications. The cohort is followed-up by means of biennial mailed questionnaires that inquire about lifestyle practices and other exposures of interest, as well as the incidence of newly diagnosed disease. The population for the current analysis was limited to the 37,999 men who answered the 1994 long-form questionnaire, which included a question about family history of kidney stones.

Assessment of Family History

On the 1994 questionnaire, all participants were asked if either parent or any of their siblings had ever had a kidney stone. The relatives of the participants were not contacted by the investigators.

Assessment of Diet

Diet was assessed in 1986 and 1990 using a semiquantitative food-frequency questionnaire that inquired about the average use of 131 foods and beverages during the previous year. Nutrient intake was computed from the reported frequency of consumption of each specified unit of food or beverage and from published data on the nutrient content of the specified portions (10). Information was also collected on supplemental vitamins and minerals, including calcium (such as calcium carbonate), either alone or in multivitamin preparations. We have previously reported on the reproducibility and validity of this dietary questionnaire in this cohort (11).

Nutrient values were adjusted for total energy intake using a regression model with total caloric intake as the independent variable.
and absolute nutrient intake as the dependent variable (12). Because total energy intake for an individual tends to be fixed in a narrow range, changes in nutrient intake must be made primarily by altering the composition of the diet, not the total amount of food consumed. Energy-adjusted values reflect the nutrient composition of the diet independent of the total amount of food consumed. In addition, energy-adjustment reduces any variation introduced by underreporting or overreporting of intake on the food frequency questionnaire, thus improving the accuracy of nutrient measurement (11).

24-H Urine Collections
In 1994, we invited participants with incident stones confirmed by supplementary questionnaire and a random sample of control subjects to provide a 24-h urine collection. Participants were ineligible for the urine collection study if they were older than 70 yr of age, had a history of cardiovascular disease or cancer, had their first stone prior to 1988, or did not respond to the 1994 biennial questionnaire. We chose not to request urine from men who had stones in the very distant past and thus excluded men from the urine collection who had their incident stone between 1986 and 1988. The men were asked to collect their urine for measurements of calcium, citrate, oxalate, potassium, and other factors, using a collection system developed by Mission Pharmacal (San Antonio, TX), which can be mailed to participants and then returned by mail to Mission for analysis. The men were sent a 4-L jug with a lithium-impregnated sponge attached to the bottom and were asked to collect all of their urine in the jug during a 24-h period. At the completion of the collection, samples were poured into two small vials, which were provided. These vials were placed in a self-addressed stamped mailer and returned to Mission. The laboratory measurements were performed by technicians at Mission Pharmacal who were blinded to the individuals’ exposures and case status. Total volume is calculated from the concentration of lithium in the samples. In 1994, 79% of eligible men with confirmed stones and 59% of control subjects agreed to participate, and the collections were completed by 302 (77%) and 95 (81%), respectively. Sixteen men with incomplete collections, determined by total urinary creatinine excretion of less than 1000 mg/d or total urine volume of less than 400 mL/d, and 12 with missing family history information were excluded from the analysis using the urine data, leaving a total of 369 samples. Based on supplementary information provided by the case subjects, less than 10% of the case subjects who performed the urine collection were being treated with medication to prevent stone recurrence.

Follow-Up and Case Ascertainment
We sent follow-up questionnaires to the entire cohort in 1988, 1990, 1992, and 1994, inquiring about kidney stones diagnosed since January 1986. After up to six mailings for each follow-up period, the response rate averaged 94% for each mailing cycle.

Prevalent cases were considered those that occurred before 1986. We considered incident cases those that occurred during the first 8 yr of follow-up, between the return of the 1986 baseline questionnaire and January 31, 1994. If a kidney stone was reported on a follow-up questionnaire, then a supplementary form was mailed to confirm the self-report and to ascertain the date of occurrence and symptoms. The response rate to the supplementary questionnaire for each 2-yr period was over 92%. The primary end point was an incident kidney stone accompanied by pain or hematuria. To confirm the validity of the self-report, we obtained the medical records from a random sample of 60 of the confirmed cases. The records confirmed the diagnosis of a kidney stone in 97% of the cases; the remaining 3% were bladder stones.

Statistical Analyses
For each participant, the person-months of follow-up were counted from the date of the return of the 1986 questionnaire to the date of a kidney stone or death, or January 31, 1994, whichever came first. Information on exposures of interest from the 1986 questionnaire was updated in 1990. We allocated person-months of follow-up according to exposure status at the start of each follow-up period (e.g., indicated by the quintile of calcium intake and other variables) and calculated incidence as the number of events divided by the person-time of follow-up. If complete dietary information was missing at the start of a time period, the subject was excluded for that time period.

The relative risk—the incidence rate in a particular category of exposure divided by the corresponding rate in the comparison category—was used as the measure of association. Age-adjusted relative risks were calculated after stratification by 5-yr age categories. The Mantel extension test was used to evaluate linear trends across categories of nutrient intake. In addition, relative risks were adjusted simultaneously for potentially confounding variables, using a proportional-hazards model (13). The variables considered in these models were age (5-yr categories), geographic region (seven categories), use of thiazide diuretics (yes/no), alcohol intake (seven categories), body mass index (six categories), quintiles of total fluid intake, supplemental calcium intake (none, 1 to 100 mg/d, 101 to 500 mg/d, and >500 mg/d) and quintiles of energy-adjusted dietary intake of calcium, animal protein, sucrose, magnesium, sodium, potassium, and caffeine. Separate logistic regression models were run after stratifying the men according to family history of kidney stones. Logistic models were also run using the raw nutrient values without energy-adjustment. For all relative risks, we calculated 95% confidence intervals (CI).

Categorical comparisons were performed using Fisher’s exact test, and confidence intervals were calculated using the RBV variance (StatXact, Cambridge, MA). Continuous variables were compared using the t test (SAS Institute, Cary, NC). All P values are two-tailed.

Results
Of the 37,999 men providing information in 1994, a family history of kidney stones was reported by 4873 (12.8%).

Prevalent Stones
In 1986, 2957 (7.8%) men had a personal history of kidney stones. A family history of kidney stones was reported by 17.2% of men who had a kidney stone before 1986, compared with 6.4% of men who had never had a stone (age-adjusted odds ratio = 3.16; 95% CI, 2.90 to 3.45) (Table 1).

Incident Stones
For the analyses of incident stones occurring between 1986 and 1994, we excluded men with a personal history of kidney stones at baseline and limited the analyses to the 34,501 men with information on diet and family history. Age-adjusted characteristics of this group of men, stratified by family history, are shown in Table 2. Men with and without a family history were very similar with respect to age, daily dietary intake, body mass index, and thiazide use. During 264,835 person-years of follow-up over an 8-yr period, we documented 795 incident cases of symptomatic kidney stones. After adjustment for age, a family history of kidney stones was associated with a increased risk of stone formation (Table 3). The relative risk for men with a positive
family history of kidney stones, compared with those without, was 2.64 (95% CI, 2.26 to 3.08). Adjustment for other potential risk factors only slightly attenuated the increased risk. After adjusting for age, use of thiazide diuretics, alcohol, body mass index, and energy-adjusted dietary intake of calcium, animal protein, sodium, potassium, sucrose, caffeine and fluid, the relative risk of incident stone formation in men with a positive family history of kidney stones, compared with those without, was 2.57 (95% CI, 2.19 to 3.02).

The magnitude of the association between family history and incident stone formation was significantly greater in men younger than 60 yr of age (RR = 2.88) than in those men 60 yr of age and older (RR = 1.74; test for interaction, \( P = 0.026 \)) (Table 3).

Table 2. Age-adjusted characteristics of the 34,501 men with no personal history of kidney stones in 1986, according to family history of kidney stones*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Personal history of kidney stones (%)</th>
<th>Age-adjusted odds ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family History of Kidney Stones</td>
<td>Yes (n = 3951)</td>
<td>3.05 (95% CI, 2.79 to 3.32)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No (n = 31,008)</td>
<td>3.16 (95% CI, 2.90 to 3.45)</td>
<td></td>
</tr>
</tbody>
</table>

To examine whether the impact of dietary risk factors varies by the presence or absence of family history of stones, we studied the association between nutrient intake and risk of incident kidney stones, stratified by family history. The results presented are for the relative risks in the highest quintile of intake of the specific nutrient, compared with the lowest quintile (Table 4). Family history did not significantly modify the inverse association between the intake of dietary calcium or potassium and the risk of incident kidney stones. The risk of stone formation in men in the highest, compared with the lowest, quintile of dietary calcium intake was 0.59 (95% CI, 0.35 to 0.98) for men with a family history and 0.72 (95% CI, 0.55 to 0.96) for men without. Supplemental calcium intake was not associated with risk, and this did not differ by family history. The risk of stone formation in men in the highest, compared with the lowest, quintile of potassium intake was 0.45 (95% CI, 0.33 to 0.62) for men with a family history and 0.49 (95% CI, 0.33 to 0.69) for men without. The magnitude of the risks for animal protein and sodium intake appeared to be higher in men with a family history, but these were not statistically different from the risks in men without. Caffeine and fluid intake were significantly inversely associated with risk of incident stone formation only in men without a family history, but the estimates were only marginally significantly different from those with a family history (tests for interaction, \( P_{\text{caffeine}} = 0.06 \) and \( P_{\text{fluid}} = 0.09 \)).
Table 4. Multivariate relative risks for incident kidney stones in the highest, compared with the lowest, quintile of energy-adjusted nutrient intake among 34,501 men, according to family history of kidney stones

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Daily Intake*</th>
<th>Relative Riskb (95% CI) by Family History of Kidney Stones</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium, dietary (mg)</td>
<td>Highest Quintile</td>
<td>Lowest Quintile</td>
</tr>
<tr>
<td></td>
<td>≥1002</td>
<td>≤555</td>
</tr>
<tr>
<td>Animal protein (g)</td>
<td>≥81.4</td>
<td>≤53.4</td>
</tr>
<tr>
<td>Sodium (mg)</td>
<td>≥3979</td>
<td>≤2369</td>
</tr>
<tr>
<td>Potassium (mg)</td>
<td>≥3992</td>
<td>≤2854</td>
</tr>
<tr>
<td>Sucrose (g)</td>
<td>≥67</td>
<td>≤32</td>
</tr>
<tr>
<td>Caffeine (mg)</td>
<td>≥581</td>
<td>≤26</td>
</tr>
<tr>
<td>Fluid (ml)</td>
<td>≥2544</td>
<td>≤1274</td>
</tr>
<tr>
<td>Calcium, supplemental (mg)</td>
<td>&gt;500</td>
<td>0</td>
</tr>
</tbody>
</table>

a For illustrative purposes, cutpoints for the dietary variables are from the 1986 questionnaire. However, the period-specific values were used for the full 1986-1994 analyses.

b The relative risk is the risk of incident kidney stone formation in the men in the highest quintile of intake, compared with the lowest quintile. The multivariate model included age (in 5-yr age categories), use of thiazide diuretics (yes or no), alcohol (seven categories), body mass index (six categories), supplemental calcium intake (four categories), and dietary intake of the listed variables (quintile groups). CI, confidence interval.

The results of the logistic models using the raw nutrients differed very little from energy-adjusted models. The only substantial change were the relative risks for caffeine—0.72 (95% CI, 0.43 to 1.20) for men with a family history and 0.73 (95% CI, 0.53 to 0.99) for men without a family history.

24-H Urine Values

The means (± SD) of the 24-h urine values in 369 men according to family history and case status are shown in Table 5. Among men with incident stones ("cases"), those with a family history of stones had significantly higher mean 24-h urinary calcium and citrate excretion. Among men without a family history, the cases excreted significantly more calcium and phosphorus, less potassium and total volume, and had significantly higher calcium oxalate supersaturation. Although among men with a family history the cases appeared to excrete more calcium and citrate and to have higher calcium oxalate supersaturation, the results were not significantly different from the controls.

Discussion

These data support previous observations that men who have suffered from kidney stones are approximately three times more likely to have a family history of kidney stones. A family history of kidney stones also substantially increases the risk of stone formation in men who never have had a stone, independent of their dietary intake. The magnitude of the association between family history and risk of stones was greater in men younger than 60 yr of age. However, there were no strong interactions between family history and nutrient intakes. In particular, family history did not modify the inverse association between dietary calcium intake and the risk of incident stone formation.

Several genetic factors are likely to play a role in calcium oxalate stone disease and may result in abnormal excretion of calcium, uric acid, citrate, inhibitors, or promoters (6). The inheritance of these factors appears to be polygenic (1,6), although there have been reports of rare families that are consistent with autosomal monogenic dominant (7) and X-linked recessive (14) patterns.

Hypercalciuria is the abnormality most commonly identified with a family history of stones. However, not all hypercalciuric individuals have a family history of kidney stones and not all patients with stones and a family history are hypercalciuric. Calcium restriction has been recommended for some patients with hypercalciuria and stones, with the goal of decreasing urinary calcium excretion. However, calcium restriction actually may increase the risk of stone formation even in patients with hypercalciuria, potentially because of the increase in gastrointestinal absorption of oxalate (15). Because our information on 24-h urinary calcium excretion represents only a subset of our cohort, the interaction between hypercalciuria and dietary calcium intake cannot be specifically addressed. Nevertheless, our results suggest that a higher dietary calcium intake decreases the risk of stone formation to a similar degree in men with and without a family history. In addition, calcium supplement use was not associated with risk in either category of family history. The lack of an association between calcium supplement use and stone risk may be due to several factors, such as increased urinary calcium excretion, the timing of ingestion (typically not with meals), and increased citrate ex-
Table 5. Twenty-four-hour urine values (means ± SD) among 369 men with and without incident kidney stone formation, according to family history of kidney stones*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Family History</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Yes</td>
<td>No</td>
<td>Cases (n = 209)</td>
<td>Controls (n = 73)</td>
</tr>
<tr>
<td>Age, 1994 (yr)</td>
<td></td>
<td>57.0 ± 7.2</td>
<td>58.6 ± 7.5</td>
<td>57.5 ± 7.1</td>
<td>60.6 ± 6.8</td>
</tr>
<tr>
<td>Body mass index, 1994 (kg/m²)</td>
<td></td>
<td>26.0 ± 2.8</td>
<td>29.1 ± 4.4</td>
<td>26.1 ± 3.6</td>
<td>26.2 ± 3.5</td>
</tr>
<tr>
<td>Calcium (mg)</td>
<td></td>
<td>264 ± 114</td>
<td>201 ± 104</td>
<td>229 ± 119</td>
<td>184 ± 102</td>
</tr>
<tr>
<td>Oxalate (mg)</td>
<td></td>
<td>47 ± 14</td>
<td>45 ± 10</td>
<td>46 ± 14</td>
<td>44 ± 12</td>
</tr>
<tr>
<td>Sodium (mg)</td>
<td></td>
<td>194 ± 72</td>
<td>211 ± 84</td>
<td>190 ± 70</td>
<td>183 ± 76</td>
</tr>
<tr>
<td>Potassium (mg)</td>
<td></td>
<td>82 ± 27</td>
<td>84 ± 26</td>
<td>75 ± 25</td>
<td>85 ± 26</td>
</tr>
<tr>
<td>Magnesium (mg)</td>
<td></td>
<td>133 ± 44</td>
<td>123 ± 29</td>
<td>127 ± 42</td>
<td>123 ± 36</td>
</tr>
<tr>
<td>Uric acid (mg)</td>
<td></td>
<td>741 ± 219</td>
<td>793 ± 165</td>
<td>683 ± 253</td>
<td>709 ± 203</td>
</tr>
<tr>
<td>Citrate (mg)</td>
<td></td>
<td>757 ± 330</td>
<td>684 ± 258</td>
<td>658 ± 291</td>
<td>640 ± 253</td>
</tr>
<tr>
<td>Phosphorus (mg)</td>
<td></td>
<td>1167 ± 354</td>
<td>1176 ± 278</td>
<td>1152 ± 327</td>
<td>1104 ± 267</td>
</tr>
<tr>
<td>Volume (L)</td>
<td></td>
<td>1.7 ± 0.7</td>
<td>1.9 ± 0.9</td>
<td>1.6 ± 0.6</td>
<td>1.8 ± 0.8</td>
</tr>
<tr>
<td>Supersaturation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>calcium oxalate</td>
<td></td>
<td>2.86 ± 1.35</td>
<td>2.10 ± 1.30</td>
<td>2.56 ± 1.31</td>
<td>1.82 ± 0.99</td>
</tr>
<tr>
<td>uric acid</td>
<td></td>
<td>3.05 ± 2.05</td>
<td>2.93 ± 2.01</td>
<td>2.88 ± 2.01</td>
<td>2.61 ± 1.72</td>
</tr>
<tr>
<td>sodium urate</td>
<td></td>
<td>3.81 ± 2.48</td>
<td>4.29 ± 3.26</td>
<td>3.58 ± 2.39</td>
<td>3.18 ± 2.28</td>
</tr>
</tbody>
</table>

* Twenty-four-hour urine collections were performed after the incident stone event in the cases.

\* P < 0.05 for comparison of cases with and without family history.

\*\* P < 0.05 for comparison of cases with controls without family history.

cretaion as a result of the increased alkaline load of calcium carbonate.

Hyperuricosuria may also be related to family history. Uric acid metabolism and excretion may be influenced by inherited factors (16), and men with a gouty diathesis are at increased risk of stone formation (17). In this study, the mean 24-h uric acid excretion was higher in both cases and controls in men with a positive family history, but the differences were not statistically significant.

Urinary oxalate excretion is influenced by the dietary intake of oxalate and endogenous oxalate production, but the relative contribution of these two sources remains controversial. Although there are recognized genetic disorders resulting in a dramatic overproduction of oxalate, such as primary hyperoxaluria (18), the vast majority of stone formers have urinary oxalate levels that are modestly elevated or in the normal range.

Hypocitraturia is also a risk factor for calcium oxalate stone disease. Surprisingly, urinary citrate levels were significantly higher in the cases with a family history. It is unlikely that this difference occurs as a result of treatment because very few men were being medically treated for their stone disease. We are unaware of other published data on urinary citrate excretion and family history.

To decrease the likelihood of stone formation, patients are routinely advised to increase their urine volume by increasing their fluid intake. We have previously shown an inverse association between total fluid intake and risk of stone formation (19). In addition, caffeine use would be expected to result in a more dilute urine, and thus lower the risk, by interfering with the action of antidiuretic hormone in the distal nephron (20). It is unclear why fluid intake and caffeine were not associated with reduced risk in men with a family history but were associated in men without a family history. These findings perhaps provide a clue for how family history might influence the risk of stone formation.

Despite the strong association between family history and kidney stones, most individuals who have kidney stones do not have a family history. In our cohort, 72% of the prevalent cases and 74% of the incident cases did not have a family history of kidney stones. Although the magnitude of the risk of incident stone formation associated with family history was much higher than for any of the individual dietary factors, the majority of stone formers did not have a family history. Thus it is likely that dietary factors—in particular, the intake of calcium, animal protein, and potassium—play a more important role in stone formation than family history among most patients who form stones.

There are potential explanations, other than genetic, for the observed increased risk associated with a positive family history. The family history information was collected in 1994, after all of the cases had occurred. Thus there may have been reporting bias because individuals who have had a stone may have been more likely to search out a history in family members. However, this is unlikely because our results are consistent with previous reports in which family members themselves
were contacted about their history (1). Another possible explanation is that individuals with a family history were more likely to share similar environmental exposures that predispose to stone formation, such as dietary factors (9) or geographic region (21). However, in our cohort, family history remained independently associated with risk even after controlling for dietary factors and geographic region. Biased recall of diet was avoided because the dietary information was collected before the diagnosis was made. The potential for information bias is avoided because the dietary information was collected before the diagnosis was made. The potential for information bias is also unlikely to explain the observed associations between the dietary factors and risk within strata of family history.

These results are generalizable to men aged 40 yr and older. The age-specific incidence rates were stable between the ages of 40 to 59 (data not shown), suggesting that these findings may apply to younger men as well. Whether these results apply to women remains to be studied, but family history also appears to be an important risk factor in women (2).

In conclusion, our results support the belief that a family history of kidney stones substantially increases the risk of stone formation. Family history does not appear to influence the association between a high dietary calcium intake and reduced risk of stone formation. Therefore, dietary calcium restriction may increase the risk of stone formation, even among individuals with a family history of kidney stones.

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References