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Impact of Nutritional Factors on Incident Kidney Stone Formation: A Report From the WHI OS

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Abstract

Purpose—Increased fluid intake, and decreased dietary sodium and animal protein intake are thought to reduce the risk of kidney stones but the role of calcium intake is controversial. We evaluated the relationship between dietary factors and incident kidney stone formation.

Materials and Methods—Secondary analysis was done of 78,293 women from the prospective WHI OS (Women's Health Initiative Observational Study) with no history of nephrolithiasis who completed the validated food frequency questionnaire. Multivariate logistic regression was used to determine demographic and dietary factors, and supplement use independently associated with incident kidney stones.

Results—Overall 1,952 women (2.5%) reported an incident kidney stone in 573,575 person-years of followup. The risk of incident kidney stones was decreased by 5% to 28% ($p = 0.01$) with higher dietary calcium intake and by 13% to 31% ($p = 0.002$) with higher water intake after adjusting for nephrolithiasis risk factors. Conversely higher dietary sodium intake increased the risk of nephrolithiasis by 11% to 61% ($p < 0.001$) after adjustment with the most pronounced effect in women with the highest intake. Higher body mass index independently increased the risk of

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incident nephrolithiasis (adjusted OR 1.19–2.01, p <0.001). Animal protein intake was not associated with nephrolithiasis on multivariate analysis.

Conclusions—This study adds to the growing evidence underscoring the importance of maintaining adequate fluid and dietary calcium intake. Greater dietary calcium intake significantly decreased the risk of incident kidney stones. In contrast, excess sodium intake increased the risk of incident nephrolithiasis, especially in women with the highest intake. Animal protein intake was not independently associated with nephrolithiasis.

Keywords

kidney; kidney calculi; sodium; dietary; calcium; dietary; nutrition disorders

Dietary modifications are some of the most accessible and requested interventions in the hope of decreasing the risk of kidney stones. Before a complete metabolic stone evaluation recommendations generally include increased fluid intake, decreased dietary sodium intake and decreased animal protein intake at individual meals.[1–3]

Since most kidney stones are composed of calcium oxalate (65% to 70%) or calcium phosphate (16% to 20%), much research has focused on decreasing the urinary excretion of calcium and oxalate.[4] Although it was originally believed that a high calcium intake increased the risk of nephrolithiasis, there is growing evidence that higher dietary calcium intake may reduce the risk of kidney stones by 35% to 50%.[5,6] This protective effect may be due to the binding of calcium with intestinal oxalate, thus, decreasing oxalate absorption and subsequent urinary excretion.[2,7,8] Many groups believe that calcium supplementation may increase the risk of nephrolithiasis by providing an isolated calcium load in the absence of intestinal oxalate so that recommendations to increase calcium supplementation for patients with a history of kidney stones are currently controversial.[5,6]

In small studies using 24-hour urine collection increased sodium intake was associated with increased urinary calcium excretion.[9–11] In the distal nephron, which is the primary site of renal calcium transport regulation, sodium and calcium excretion are related in that an increased sodium load increases urinary calcium.[12] Thus, excess sodium intake is believed to predispose to hypercalciuria and may increase the risk of nephrolithiasis.[13] However, we recently reported that calcium oxalate supersaturation decreased with oral sodium supplementation, suggesting that the hypercalciuric effect of increased sodium intake may be offset by increased voluntary fluid intake.[14]

A diet rich in animal protein is believed to increase the risk of kidney stones. A meal composed primarily of animal protein may cause postprandial metabolic acidosis, resulting in calcium and phosphate resorption from the bones.[15] Excess animal protein intake is thought to cause transient urinary acidification with subsequent decreased urinary citrate and increased undissociated uric acid excretion.[3] Animal protein intake may also directly contribute to endogenous oxalate synthesis.[16]

The primary purpose of this study was to examine the association of calcium, sodium and protein intake, and the risk of incident kidney stones using data from participants in WHI

OS. We hypothesized that increased dietary calcium intake would decrease the risk of incident nephrolithiasis while increased sodium and protein intake would increase the risk of nephrolithiasis.

MATERIALS AND METHODS

The prospective WHI OS enrolled 93,767 postmenopausal women 50 to 79 years old from 1993 to 1998 who were followed an average of 8 years. Details on WHI OS rationale, design and eligibility were reported previously.[17] Briefly, participating women completed health history questionnaires at enrollment and at 1-year intervals during followup. Demographic, medical history and anthropomorphic information was collected. The history of nephrolithiasis was first assessed in year 3. Incident kidney stone episodes were then self-reported annually through year 8. The validated WHI food frequency questionnaire was administered to participants at study enrollment.[18]

We excluded from analysis 14,166 women who did not complete the food frequency questionnaire or who completed the questionnaire incorrectly or incompletely (a missing, partially complete or extreme reported energy intake of less than 600 or greater than 5,000 kcal daily) as well as 1,308 who reported a history of nephrolithiasis at the first assessment in year 3 since they may have altered the diet in response to this diagnosis. We performed secondary analysis of a final population of 78,293 women.

Our primary aim was to evaluate the relationship between incident nephrolithiasis, and dietary calcium, sodium and protein intake. Age was analyzed as a continuous variable. BMI was evaluated categorically (less than 18.5, 18.5 to 24.9, 25 to 29.9, 30 to 34.9, 35 to 39.9 and 40 kg/m^2 or greater). Education served as a surrogate for socioeconomic status and was analyzed categorically (high school or less, some college, college degree, graduate degree and professional degree). Geographic region was categorized as Northeast, South, Midwest and West. Dietary calcium, sodium and protein intake was estimated from intakes reported on the food frequency questionnaires and categorized into quintiles. Women who supplemented calcium were placed into 5 categories (none and 4 daily dose quartiles).

Chi-square analysis was done to compare categorical variables between patients with vs without incident nephrolithiasis. The Student t test was used to compare continuous variables and the Wilcoxon rank sum test was applied to compare medians. The Pearson correlation was used to compare dietary sodium and water intake. The rate of incident kidney stone formation was determined by comparison to the total number of women participating at each followup visit. Multivariate logistic regression analysis was done to evaluate factors independently associated with incident kidney stones with a priori adjustment for age, race/ethnicity, education, geographic region, calcium supplementation category and estrogen use. The OR, adjusted OR and 95% CI were determined. All p values were 2-tailed and statistical significance was considered at $p < 0.05$. Analysis was done using SAS® 8.0.

Our study received University of California institutional review board exemption. For the original WHI OS the appropriate institutional review board approvals were obtained at all participating institutions and written informed consent was obtained from all participants.

RESULTS

Of the 78,293 women 1,952 (2.5%) without a history of kidney stones reported incident nephrolithiasis during 573,575 person-years of followup. There were significant differences between participants with and without incident kidney stones in race, BMI, education and history of hypertension.

There was considerable variability in participant average daily intake of water, calcium, sodium and animal protein. Daily water intake was slightly lower in women in whom kidney stones developed during the study period (mean 1.45 ± 0.65 vs 1.51 ± 0.62 l, $p < 0.001$).

Average daily dietary calcium intake was 39 mg lower in women with incident nephrolithiasis (mean 769 ± 456 vs 808 ± 453, $p < 0.001$). Mean daily sodium intake was 60 mg higher in women in whom new kidney stones developed (2,577 ± 1,152 vs 2,517 ± 1,045 mg, $p = 0.01$). Daily animal protein intake was slightly higher in women with incident kidney stones (mean 47 ± 25 vs 45 ± 22 gm, $p = 0.005$) while mean total protein intake was similar between the groups ($p = 0.14$). Calcium supplementation was less common in women in whom new kidney stones developed (67% vs 73%, $p = 0.02$) and the amount of supplemental calcium was lower in those in whom incident kidney stones developed (mean 613 ± 433 vs 646 ± 435 mg daily, $p = 0.01$). Dietary sodium and water intake correlated moderately ($r = 0.57$).

On unadjusted analysis total calcium intake decreased the risk of kidney stones by 25% to 36% ($p < 0.001$, table 1). The risk of incident kidney stones decreased 14% to 48% as the dietary calcium quintile increased ($p < 0.001$). On the other hand, there was a 13% to 75% increased risk of incident kidney stones as sodium intake increased ($p < 0.001$), especially for women with the highest daily intake of sodium. Total protein and animal protein intake was variably associated with nephrolithiasis. Increased water intake decreased the risk of incident nephrolithiasis by 20% to 39% ($p < 0.001$).

Dietary calcium and sodium, water intake and BMI were independently associated with incident nephrolithiasis after adjusting for age, race/ethnicity, education, geographic region, calcium supplementation and current estrogen use (table 2). Increasing quintile of dietary calcium was associated with a 5% to 28% decreased risk of kidney stones after adjustment ($p = 0.01$). Increasing quintile of dietary sodium intake was associated with an 11% to 61% increased risk of nephrolithiasis (p for trend < 0.001) with the most pronounced effect in women with the highest sodium intake. Increasing water intake decreased the risk of incident kidney stone formation by 13% to 31% after adjustment ($p = 0.002$). Increasing BMI category was associated with a 1.19 to 2.01-fold increased risk of nephrolithiasis after adjustment ($p < 0.001$). Dietary animal protein intake was not independently associated with incident kidney stones on multivariate analysis ($p = 0.12$).

DISCUSSION

Dietary modifications are some of the most accessible interventions to potentially decrease the risk of kidney stones. Patients frequently ask what dietary interventions are helpful and would rather alter the diet than be burdened with a lifetime of prescription medications.[19] We hypothesized that increased dietary calcium intake would decrease the likelihood of nephrolithiasis while increased sodium and protein intake would increase the risk of kidney stones.

In our study increased dietary calcium intake was associated with a 5% to 28% decreased risk of kidney stones after adjusting for known nephrolithiasis risk factors. There was a steady incremental decrease in the risk of kidney stones as dietary calcium intake increased. This is consistent with previous large epidemiological studies of men 40 to 75 years old and younger women 34 to 59 years old, which demonstrated a 27% to 35% decreased risk of kidney stone formation after adjustment when comparing the highest and lowest quintiles of dietary calcium intake.[1,5,6,20] Thus, this protective effect of dietary calcium appears to be unrelated to age, gender or menopausal status and may be related to greater intestinal binding of oxalate, thereby decreasing oxalate absorption and decreasing urinary oxalate excretion. In our study approximately 80% of the women consumed less than the Institute of Medicine recommended daily dietary calcium intake of 1,000 to 1,200 mg,[21] which may have further predisposed some of them to kidney stones.

Dietary sodium intake was associated with an 11% to 61% increase in the risk of kidney stones after adjusting for other nephrolithiasis risk factors. This effect was most pronounced in women with the highest daily sodium intake of greater than 3,249 mg. This finding confirms a report from the Nurses' Health Study I suggesting a 30% increased risk (RR 1.30, 95% CI 1.05–1.62) of kidney stones in women with the highest sodium intake after adjusting for other risk factors.[6] These findings are consistent with physiological studies showing that excess sodium intake is associated with increased urinary excretion of sodium and calcium, and subjects who consumed the highest levels of sodium tended to have the greatest urinary calcium excretion.[9–11] Indeed, more than 80% of the women in this study exceeded the recommended daily adequate intake of sodium (1,600 mg) and more than 40% exceeded the upper limit of daily sodium intake (2,300 mg).[21]

Possibly the risk of excess sodium in regard to kidney stone formation was attenuated in this study due to increased water intake, as supported by our finding of a modest correlation between the 2 variables ($r = 0.57$).[14] If dietary sodium intake and fluid intake correlate, some of the stone risk due to excess sodium intake might be partially offset by a corresponding increase in fluid intake. This might ultimately lead to a slight decrease in the urinary supersaturation of all stone types.

Excessive animal protein intake is believed to predispose to uric acid and calcium based kidney stones. However, in this study animal protein intake did not appear to increase the risk of kidney stones on univariate or multivariate adjusted analysis. A possibility is that animal protein intake contributes to kidney stone development in only a minority of patients.

Alternatively dietary animal protein intake may be less important for nephrolithiasis development than previously asserted.

Consistent with prior studies, increasing BMI category was associated with an increased risk of kidney stones.[22–25] This finding adds to the growing literature demonstrating that the risk of kidney stones is increased in patients with obesity, in addition to the other components of metabolic syndrome such as hypertension, diabetes mellitus, increased total cholesterol and decreased high density lipoprotein cholesterol.[26,27] We also recently reported a positive association between kidney stones and carotid artery disease.[28] Consequently given the potential interrelatedness of cardiovascular disease and nephrolithiasis, successful implementation of dietary modifications in patients with kidney stones might provide the additional benefit of decreasing the risk of cardiovascular disease.

Calcium supplementation was less common among women in whom nephrolithiasis developed during the study period. The Nurse's Health Study I and a recent WHI randomized, controlled trial of calcium and vitamin D supplementation revealed a 17% to 20% increased risk of kidney stones with calcium supplementation.[6,29,30] In contrast, observational studies such as the Nurse's Health Study II and a prospective study of 45,619 men showed no increased risk of nephrolithiasis with calcium supplementation.[1,5,20] Overall it is likely that calcium supplements, especially when taken without a meal containing oxalate, provide an isolated calcium load that predisposes to nephrolithiasis.

To our knowledge this study is the largest of its kind to describe risk factors for nephrolithiasis in participants from a broad, diverse cross-section of the American population. However, the study has limitations. Our population was limited to post-menopausal women and, thus, findings may not be applicable to men or premenopausal women. Excluding participants with a history of kidney stones eliminated more than 1,300 women from analysis. However, this exclusion allowed us to determine factors related to the development of incident kidney stones, potentially decreased the time from collecting dietary information and the stone event, and lessened the confounding effect of any prior dietary counseling that patients may have received in response to a previous diagnosis of urinary stone disease. Women may have completed the validated food frequency questionnaire incorrectly despite our efforts to exclude those with an incomplete, incorrect or extreme caloric energy intake. Corresponding 24-hour urinary parameters were not measured. While our findings imply a significant relationship between calcium and sodium intake, and kidney stone formation, confirmatory studies showing correlative changes in urinary parameters could be valuable.

CONCLUSIONS

This large study indicates that dietary calcium intake independently decreases the risk of nephrolithiasis. Excessive sodium intake increases the risk of kidney stones. Animal protein intake did not appear to be associated with incident kidney stones and an emphasis on reduced animal protein intake may not be as clinically relevant. Increased BMI was associated with an increased risk of nephrolithiasis. These factors may be clinically important targets for intervention to help decrease the risk of kidney stones.

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Abbreviation and Acronym

BMI body mass index

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Table 1

Unadjusted risk of incident kidney stones

Intake	OR (95% CI)	p Value
Total calcium (quartile):		
Lowest	Referent	<0.001
2nd	0.75 (0.66–0.85)	
3rd	0.70 (0.61–0.80)	
Highest	0.64 (0.56–0.73)	
Dietary calcium (quintile):		
Lowest	Referent	<0.001
2nd	0.86 (0.75–0.99)	
3rd	0.69 (0.59–0.81)	
4th	0.60 (0.51–0.72)	
Highest	0.52 (0.43–0.62)	
Dietary sodium (quintile):		
Lowest	Referent	<0.001
2nd	1.13 (0.98–1.32)	
3rd	1.15 (0.98–1.34)	
4th	1.13 (0.95–1.34)	
Highest	1.75 (1.46–2.08)	
Animal protein (quintile):		
Lowest	Referent	0.03
2nd	0.97 (0.83–1.12)	
3rd	0.95 (0.82–1.10)	
4th	0.87 (0.82–1.01)	
Highest	1.11 (0.96–1.28)	
Water (quintile):		
Lowest	Referent	<0.001
2nd	0.80 (0.69–0.91)	
3rd	0.75 (0.64–0.85)	
4th	0.61 (0.52–0.70)	
Highest	0.74 (0.64–0.85)	

Table 2

Factors independently associated with incident kidney stones

	Adjusted OR (95% CI)*	p Value
Dietary calcium intake (quintile):		
Lowest	Referent	0.01
2nd	0.95 (0.81–1.11)	
3rd	0.83 (0.70–0.98)	
4th	0.76 (0.63–0.92)	
Highest	0.72 (0.58–0.88)	
Dietary sodium intake (quintile):		
Lowest	Referent	<0.001
2nd	1.11 (0.95–1.30)	
3rd	1.17 (0.98–1.39)	
4th	1.13 (0.94–1.37)	
Highest	1.61 (1.32–1.96)	
Water intake (quintile):		
Lowest	Referent	0.002
2nd	0.87 (0.75–1.02)	
3rd	0.83 (0.71–0.98)	
4th	0.69 (0.57–0.82)	
Highest	0.80 (0.66–0.96)	
BMI (kg/m^2):		
Less than 18.5	0.61 (0.33–1.15)	<0.001
18.5–24.9	Referent	
25–29.9	1.19 (1.06–1.35)	
30–34.9	1.58 (1.37–1.82)	
35–39.9	1.84 (1.52–2.22)	
40 or Greater	2.01 (1.60–2.53)	

* Adjusted for age, race/ethnicity, education, geographic region, calcium supplementation and current estrogen use.