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Dietary Intake of Fiber, Fruit and Vegetables Decreases the Risk of Incident Kidney Stones in Women: A Women's Health Initiative Report

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Abbreviations and Acronyms

BMI = body mass index

FFQ = food frequency questionnaire

WHI = Women's Health Initiative

Purpose: We evaluated the relationship between dietary fiber, fruit and vegetable intake, and the risk of kidney stone formation.

Materials and Methods: Overall 83,922 postmenopausal women from the Women's Health Initiative observational study were included in the analysis and followed prospectively. Cox proportional hazards regression analyses were used to evaluate the associations between total dietary fiber, fruit and vegetable intake, and the risk of incident kidney stone formation, adjusting for nephrolithiasis risk factors (age, race/ethnicity, geographic region, diabetes mellitus, calcium supplementation, hormone therapy use, body mass index and calibrated caloric intake; and dietary water, sodium, animal protein and calcium intake). Women with a history of kidney stones (3,471) were analyzed separately.

Results: Mean age of the women was 64±7 years, 85% were white and 2,937 (3.5%) experienced a kidney stone in a median followup of 8 years. In women with no history of kidney stones higher total dietary fiber (6% to 26% decreased risk, $p < 0.001$), greater fruit intake (12% to 25% decreased risk, $p < 0.001$) and

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greater vegetable intake (9% to 22% decreased risk, $p=0.002$) were associated with a decreased risk of incident kidney stone formation in separate adjusted models. In women with a history of stones there were no significant protective effects of fiber, fruit or vegetable intake on the risk of kidney stone recurrence.

Conclusions: Greater dietary intake of fiber, fruits and vegetables was associated with a reduced risk of incident kidney stones in postmenopausal women. The protective effects were independent of other known risk factors for kidney stones. In contrast, there was no reduction in risk in women with a history of stones.

Key Words: nephrolithiasis, urinary calculi, vegetables, fruit, dietary fiber

KIDNEY stone prevalence has increased by almost 70% during the last 15 years.¹ Recommendations of increased fluid intake, and low sodium, low animal protein and normal calcium intake diets have been the mainstays of the prevention of kidney stone recurrence.²⁻⁴ The identification of additional dietary factors associated with the risk of stone formation would be clinically beneficial.

Previous studies have shown that diets with higher fruit and vegetable intake might be associated with a lower risk of urinary stones.^{2,5} Fruits and vegetables provide an alkali load that could increase urinary citrate, a known inhibitor of stone formation.⁶⁻⁹ Dietary phytate, the most abundant form of phosphate in plants, forms insoluble complexes with calcium in the intestinal tract, inhibits crystal formation in the urine and is associated with a reduced risk of stones.¹⁰⁻¹² Greater fruit and vegetable intake might decrease the intake of dietary sodium, animal protein and total calories.²⁻⁴ Despite these potential benefits, there is some concern that greater intake of some vegetables (spinach, Swiss chard, beets and rhubarb, for example) might increase the risk of stone formation as they are known to be rich in oxalate.

Total dietary fiber may also impact stone formation as it contains nondigestible compounds including lignin and nonstarch polysaccharides which might bind to minerals and fat in the gut, leading to reduced urinary excretion of oxalate and calcium.^{10,12} However, prior studies have shown mixed results in terms of urinary calcium excretion¹³⁻¹⁶ and, thus, the association between fiber intake and stone formation is unclear.^{13,14,17}

The purpose of this study was primarily to evaluate the relationship between dietary fiber, fruit and vegetable intake, and the risk of incident kidney stone formation in women with no history of stones. Secondarily we evaluated these relationships with stone recurrence in women with a history of kidney stones.

METHODS

Participants

The Women's Health Initiative observational study is a prospective, longitudinal, multicenter study investigating

the health of postmenopausal women.^{18,19} Overall 93,676 women, 50 to 79 years old, enrolled from 1993 to 1998 and were followed for a median of 8 years. Participants completed health history questionnaires at enrollment and annually throughout participation, which included self-reported history and occurrence of incident stones. A WHI food frequency questionnaire was administered at enrollment.²⁰ Women who never answered the incident kidney stone questions, those who did not complete the FFQ and those who reported extremes of energy intake (less than 600 or greater than 5,000 kcalories daily as categorized by WHI) were excluded from these analyses (7,912 total women).²⁰ We also excluded 1,842 women who were missing their kidney stone history at baseline, leaving a final analytic cohort of 83,922 women. Included in this cohort were 3,471 women with a history of kidney stones before enrollment. These participants were considered a separate group for all analyses.

Measurements

Our primary aim was to evaluate the association between fiber, fruit and vegetable intake, and kidney stone events during the study period. Daily dietary energy and nutrient intake were determined using the WHI FFQ administered at the baseline enrollment evaluation, targeting intake in the previous 3 months (University of Minnesota Nutrient Data System for Research, Minneapolis, Minnesota).²⁰ Women were asked how often they ate 36 different fruits and 66 vegetables (never, monthly, 2 to 3 times per month, weekly, 2 times per week, 3 to 4 times per week, 5 to 6 times per week, daily or 2+ times per day) and the size of their serving. They were provided a reference for a medium portion for each fruit and vegetable (ie 1 medium banana, $\frac{1}{2}$ cup potatoes). Daily fiber (gm per day), fruit (medium portions) and vegetable intake (medium portions) was calculated from the FFQ and categorized into quintiles of intake. Dietary energy intake (kcalories per day) was analyzed as a continuous variable after calibration was performed to correct some of the bias associated with self-reported intake^{21,22} as previously described.^{23,24} Bootstrapping (500 samples) generated 95% CIs for all analyses including calibrated energy intake to account for the sample variation in calibration coefficient estimates.

Anthropometric variables including body weight and height were measured at the clinic by study staff. BMI was calculated (kg/m^2) and analyzed categorically (less than 18.5, 18.5 to 24.9, 25 to 29.9, 30 to 34.9, 35 kg/m^2 or greater)²⁵ as a nonlinear effect of BMI on stone risk was anticipated. Age was analyzed as a continuous variable. Baseline history of diabetes mellitus, calcium

supplementation, hormone therapy (none, prior, current) and geographic region (Northeast, South, Midwest, West) were analyzed categorically. Dietary water, salt, animal protein and calcium were categorized into quintiles. Dietary calcium intake and calcium supplementation were included as separate variables due to the perceived differential effect on the risk of stone formation.

Analyses

The primary outcome of interest was incident kidney stone occurrence during followup. For all comparisons, analyses were stratified by history of kidney stones before WHI study participation. The Wilcoxon rank sum test was used to compare median followup. Women were followed until the date of the stone event, or were censored at last followup or death. Cox proportional hazards regression analyses were used to compare categorical and continuous variables. Cox proportional hazards regression was also used in each of the 3 multivariate models to evaluate the association between primary variables of interest (fiber, fruit and vegetable intake) and kidney stone event. Each of the models was adjusted for nephrolithiasis risk factors (age, race/ethnicity, geographic region, diabetes mellitus, baseline calcium supplementation, hormone therapy use, calibrated dietary energy intake, and dietary intake of water, sodium, animal protein and calcium).^{24,26} A correlation matrix evaluated the potential collinearity of fiber, fruit and vegetable intake.

Hazard ratios, adjusted hazard ratios and 95% CIs were determined. All p values were 2-tailed and statistical significance was set at p <0.05. Analyses were performed using Stata/IC[®] v10 and SAS[®] version 9.1.

A final exploratory analysis was performed that included quintiles of fiber, fruit and vegetable intake (all 3 variables) in an attempt to determine if one of these variables was more strongly associated with kidney stone formation. To test for interaction, additional regression models were performed which included the product of the fiber*fruit, fiber*vegetable and fruit*vegetable intake interaction terms.

This study received institutional review board exemption (University of Washington, #HSD 45318). For the original WHI observational study, institutional review board approval was obtained at all participating institutions and written informed consent was obtained from all participants.

RESULTS

Women in our study population had a mean age of 64±7 years at enrollment, 85% were white and most women were normal weight or overweight. Hormone therapy use was common (60%). Most women had a moderate daily intake of fiber, fruits and vegetables. After a median followup of 8 years 2,937 stone events were reported, including 2,390 incident stone events in 583,464 person-years of followup (4 events per 1,000 person-years) and 547 recurrent stone events in 24,958 person-years of followup (21 events per 1,000 person-years). Women with a history of kidney stones were statistically different from women with no history of stones in terms of age, race, medical history, calcium supplementation, hormone therapy use, BMI and geographic region (see supplementary table, <http://jurology.com/>). Only 3% of the women with no history of stones had a stone develop during the study, while more than 15% of women with a history of stones reported an event during the study (p <0.001). Women with a history of kidney stones had a lower mean intake of fiber, fruits and vegetables, with the greatest proportion of women in the lowest and second lowest quintiles of intake (all p <0.001).

In unadjusted analyses fiber, fruit and vegetable intake was associated with a significant decreased risk of stone formation in women with no history of kidney stones (table 1). In contrast, women with a

Table 1. Univariate odds of kidney stone formation in postmenopausal women

Intake (quintile)	Intake Range*	No History of Nephrolithiasis		History of Nephrolithiasis	
		HR (95% CI)	p Value	HR (95% CI)	p Value
Fiber:			<0.001		0.24
Lowest	0–10.6	Ref		Ref	
Second	10.6–14.0	0.90 (0.79–1.01)		0.92 (0.77–1.10)	
Third	14.0–17.5	0.87 (0.77–0.98)		0.85 (0.70–1.02)	
Fourth	17.5–21.9	0.69 (0.61–0.79)		0.81 (0.67–0.99)	
Highest	21.9–99.4	0.77 (0.68–0.88)		0.87 (0.72–1.05)	
Fruit:			<0.001		0.23
Lowest	0–1.0	Ref		Ref	
Second	1.0–1.5	0.82 (0.73–0.93)		0.84 (0.70–1.00)	
Third	1.5–2.1	0.71 (0.63–0.81)		0.89 (0.75–1.07)	
Fourth	2.1–3.0	0.65 (0.57–0.73)		0.85 (0.70–1.03)	
Highest	3.0–11	0.71 (0.63–0.80)		0.84 (0.70–1.02)	
Vegetable:			<0.001		0.08
Lowest	0–1.2	Ref		Ref	
Second	1.2–1.7	0.84 (0.75–0.95)		0.92 (0.76–1.10)	
Third	1.7–2.4	0.79 (0.70–0.89)		0.93 (0.77–1.11)	
Fourth	2.4–3.3	0.71 (0.62–0.80)		0.81 (0.67–0.98)	
Highest	3.3–13.3	0.70 (0.62–0.80)		0.78 (0.64–0.95)	

*Fiber intake in gm per day, and fruit and vegetable intake in portions per day. The ranges are nonoverlapping.

history of kidney stones did not demonstrate a significant relationship between fiber ($p=0.24$) or fruit ($p=0.23$) intake and kidney stone occurrence, but had a borderline association with vegetable intake ($p=0.08$), especially at the highest 2 quintiles of intake.

In multivariate analyses women with no history of stones with the highest dietary fiber intake were 22% less likely (adjusted HR 0.78, 95% CI 0.67–0.92, p trend <0.001) to report an incident stone event during the study compared to women with the lowest fiber intake (table 2). In a separate model women with the highest fruit intake were 15% less likely (adjusted HR 0.85, 95% CI 0.74–0.98, p trend <0.001) to report an incident stone event compared to women with the lowest fruit intake. In a third model women with the highest vegetable intake were 22% less likely (adjusted HR 0.78, 95% CI 0.68–0.91, p trend = 0.002) to report an incident stone event compared to women with the lowest vegetable intake. Women with a history of kidney stones before study participation did not demonstrate a significant relationship between fiber ($p=0.93$), fruit ($p=0.73$) or vegetable intake ($p=0.50$) and kidney stone occurrence during the study. There was a moderate correlation between fiber and vegetable intake ($r=0.62$) and fiber and fruit intake ($r=0.59$), with less correlation between fruit and vegetable intake ($r=0.41$).

In the exploratory adjusted model that included fiber, fruit and vegetable intake, there was a trend toward higher fiber intake being associated with up to a 16% decreased risk of incident stones ($p=0.053$) in women with no history of stones. Higher fruit

intake was associated with a 4% to 18% decreased risk of incident stones ($p=0.04$) in women with no history of stones. Vegetable intake did not significantly decrease the risk of a stone occurrence ($p=0.20$). There was also no significant interaction between fiber and fruit intake ($p=0.92$), fruit and vegetable intake ($p=0.35$) or fiber and vegetable intake ($p=0.99$). In women with a history of stones before study participation, fiber, fruit and vegetable intake was not associated with a stone occurrence ($p=0.90$, $p=0.80$, $p=0.48$, respectively), and there was no significant interaction between these variables in this model.

DISCUSSION

This study demonstrated that women with the highest quintile intake of fiber, fruits and vegetables were 22%, 15% and 22% less likely to report an incident stone event, respectively, compared to women with the lowest quintile intake for postmenopausal women with no history of stones in adjusted analyses. This represents a difference of about 2 portions per day of fruits and vegetables, or an increase of 12 gm per day of fiber intake between the lowest and highest quintiles of intake. The effects of fiber, fruit and vegetable intake on stone risk appear to be independent of the traditional dietary risk factors including calories, fluid, sodium, animal protein and calcium intake. Increased intake of fruits and vegetables has been shown to increase urine volume, pH, potassium, magnesium, citrate, phytate and other stone inhibitors, resulting in a decrease in the supersaturation of calcium

Table 2. Association between fiber, fruit and vegetable intake and risk of kidney stone formation in separate adjusted regression models

Intake (quintile)	Intake Range*	No History of Nephrolithiasis		History of Nephrolithiasis	
		Adjusted HR (95% CI)†	p Value	Adjusted HR (95% CI)†	p Value
Fiber:			<0.001		0.93
Lowest	0–10.6	Ref		Ref	
Second	10.6–14.0	0.94 (0.83–1.08)		0.92 (0.76–1.12)	
Third	14.0–17.5	0.92 (0.81–1.05)		0.94 (0.77–1.14)	
Fourth	17.5–21.9	0.74 (0.63–0.86)		0.94 (0.75–1.18)	
Highest	21.9–99.4	0.78 (0.67–0.92)		0.98 (0.77–1.26)	
Fruit:			<0.001		0.73
Lowest	0–1.0	Ref		Ref	
Second	1.0–1.5	0.88 (0.77–0.99)		0.87 (0.72–1.05)	
Third	1.5–2.1	0.82 (0.72–0.93)		0.97 (0.79–1.18)	
Fourth	2.1–3.0	0.75 (0.66–0.86)		0.92 (0.74–1.15)	
Highest	3.0–11	0.85 (0.74–0.98)		0.93 (0.76–1.14)	
Vegetable:			0.002		0.50
Lowest	0–1.2	Ref		Ref	
Second	1.2–1.7	0.91 (0.80–1.03)		0.90 (0.75–1.07)	
Third	1.7–2.4	0.85 (0.74–0.96)		0.98 (0.81–1.18)	
Fourth	2.4–3.3	0.78 (0.69–0.90)		0.86 (0.71–1.05)	
Highest	3.3–13.3	0.78 (0.68–0.91)		0.85 (0.69–1.05)	

* Fiber intake in gm per day, and fruit and vegetable intake in portions per day. The ranges are nonoverlapping.

† Adjusted for age, race, region, diabetes mellitus, calcium supplementation, hormone therapy use categories, BMI categories, calibrated calorie intake, and quintiles of dietary water, sodium, animal protein and calcium intake.

oxalate and uric acid.⁶ It is also possible that women with the highest intake of fruits, vegetables and other fiber containing foods are making other healthy dietary choices, or perhaps avoiding foods that may increase the risk of stone formation.

However, this relationship did not exist in adjusted analyses for women with a history of kidney stones. The etiology of this differential effect is not entirely clear. The average consumption of fruits, vegetables and fiber was each lower in women with a history of stones, with the greatest proportion of women falling in the lowest intake categories. It is also possible that the intake of fiber, fruits and vegetables is important in initial stone formation, but may be less important for recurrence in the face of other stronger risk factors for stone formation such as BMI and the intake of fluids, sodium, animal protein and calcium. The nuances of which vegetables are high in oxalate can be confusing, and information from medical providers or internet sources is often incomplete. Therefore, patients may be globally reducing vegetable intake in an attempt to reduce their oxalate intake.²⁷ Reassuringly, this study specifically showed no increased risk of stone formation with higher vegetable intake. Previous studies of fiber, fruit and vegetable intake have been mixed,^{5,6,9,11–17} possibly in part due to a failure to stratify based on stone history.

Our findings suggest that there may be a fundamental difference between women who had their first stone during this study and those in whom stones recurred during the study. Only 3% of women with no history of stones had an occurrence compared to more than 15% of women with a history of stones. Thus, a woman who has her first kidney stone sometime in her 60s might be phenotypically different than a woman with a history of stones earlier in life. Women with a history of stones might be more likely to have a rare disorder related to stone formation (renal tubular acidosis, primary hyperparathyroidism, gouty diathesis, sarcoidosis etc), or perhaps behavior and diet are greater contributors to stone formation in the woman having her first stone later in life.

Although greater intake of fruits, vegetables and fiber was not associated with a protective effect in our recurrent stone formers, these findings should not discourage providers from supporting greater intake. These foods remain an important foundation of a healthy diet and are important for overall

health with benefits beyond stone risk reduction. Greater intake of fruits, vegetables and fiber likely contributes to decreased intake of foods that are high in calories, sodium, fat and animal protein. Importantly, subjects with a history of stones may not have had a decrease in stone formation, but those with the greatest vegetable intake did not appear to incur any additional risk.

This study has several limitations. The WHI only includes postmenopausal women and may not be generalizable to others, including younger women or men. The measurement of fruit, vegetable and fiber intake relied on the FFQ. This may be subject to recall bias and, thus, it provides an estimate of intake while true intake might be different. It is also possible that some of the intake is in the form of high oxalate containing foods which may offset some of the protective association demonstrated in this study. Water and sodium intake are likely underestimated as the values are calculated based on the total beverage and food content of these factors, but do not include additional quantities added in preparation or consumed at the table. Self-reported caloric intake is often unreliable and it is possible that our calibration may have only corrected some of the associated bias.^{21–23} Stone type and 24-hour urine composition were also not known. Stone events for women in the WHI are higher than prior population based reports, potentially due to increased rates of imaging detection of asymptomatic stones.²⁴ Stone events were not adjudicated in our study, although self-reported stone events have previously been determined to be 97% to 98% accurate.^{28,29}

CONCLUSIONS

Higher intake of fruits, vegetables and fiber is associated with a decreased risk of incident kidney stone formation in postmenopausal women, independent of the effect of BMI and other nephrolithiasis risk factors including dietary intake of water, sodium, animal protein and calcium. This protective effect was not seen in women with a history of stones. These groups may represent different phenotypes of stone formers with different risk factors.

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