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

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Abstract

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

Methods—Overall, 83,922 postmenopausal women from the WHI Observational Study were included and followed prospectively. Cox proportional hazards regression analyses evaluated the associations between total dietary fiber, fruits, 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, calibrated caloric intake, and dietary water, sodium, animal protein, and calcium intake). Women with a prior history of kidney stones (3,471 women) were analyzed separately.

Results—Mean age was 64±7 years, 85% of women were Caucasian and 2,937 women (3.5%) experienced a kidney stone occurrence in 8 years median follow-up. In women with no history of kidney stones, higher total dietary fiber (6-26% decreased risk, $p<0.001$), higher fruit intake (12-25% decreased risk, $p<0.001$), and higher vegetable intake (9-22% 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, fruits, or vegetable intake on the risk of kidney stone recurrence.

Conclusions—Greater dietary intake of fiber, fruits and vegetables were each 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.

Keywords

nutrition; diet; fiber; fruit; vegetables; healthy lifestyle; kidney stones; nephrolithiasis; urinary calculi; dietary fiber

INTRODUCTION

Kidney stone prevalence has increased by almost 70% over the last 15 years.[1] Recommending increased fluid intake, low sodium, low animal-protein and normal calcium intake diets have been the mainstays of prevention of kidney stone recurrence.[2-4] The identification of additional dietary factors that are associated with the risk of stone formation would be clinically beneficial.

Previous studies have noted that diets with higher fruit and vegetable intake might be associated with lower risk of urinary stones.[2, 5] Both 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 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 polysaccharies, 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 on urinary calcium excretion,[13-16] 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 and secondarily, to evaluate these relationships on stone recurrence in women with a history of kidney stones.

METHODS

Participants

The Women's Health Initiative (WHI) Observational Study is a prospective, longitudinal, multicenter study investigating the health of postmenopausal women.[18, 19] Overall, 93,676 women, age 50-79, 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 occurrences of incident stones. A WHI food frequency questionnaire (FFQ) was administered at enrollment.[20] Women who never answered the incident kidney stone questions, women who did not complete the FFQ, and those reporting extremes of energy intake (<600 or >5000 kcalories per day **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 prior to 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 was 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, MN).[20] Women were asked how often they ate 36 different fruits and 66 vegetables (never, monthly, 2-3 times per month, weekly, 2 times per week, 3-4 times per week, 5-6 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 (i.e. one medium banana, ½ cup potatoes). Daily fiber (g/day), fruit (medium portions), and vegetable intake (medium portions) were 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] Boot-strapping (500 samples) generated 95% confidence intervals for all analyses including calibrated energy intake to accounting for the sample variation in calibration coefficient estimates.

Anthropometric variables including body weight and height were measured at the clinic by study staff. Body mass index (BMI) was calculated (kg/m^2) and analyzed categorically (<18.5, 18.5-24.9, 25-29.9, 30-34.9, ≥35 kg/m^2)[25] as a non-linear 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 follow-up. For all comparisons, analyses were stratified by history of kidney stones prior to WHI study participation. Wilcoxon Rank-Sum was used to compare median follow-up. Women were followed until the date of the stone event or were censored at last follow-up 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 three multivariate models to evaluate the association between primary variables of interest (fiber, fruit, and vegetable intakes) 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, dietary intake of water, sodium, animal protein and calcium).[24, 26] A correlation matrix evaluated the potential co-linearity of fiber, fruit and vegetable intake.

Hazard ratios (HR), adjusted hazard ratios (aHR), and 95% confidence intervals (95% CI) were determined. All p-values were two–tailed, and statistical significance was set at $p<0.05$. Analyses were performed using Stata IC v10 (StataCorp LP, College Station, TX) and SAS version 9.1 (SAS Institute, Cary, NC).

A final exploratory analysis was performed that included quintiles of fiber, fruits, and vegetable intake (all three 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 approvals were 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 moderate daily intake of fiber, fruits, and vegetables. After a median follow-up of 8 years, there were 2,937 stone events reported, including 2,390 incident stone events in 583,464 person-years follow-up (4 events per 1000 person years) and 547 recurrent stone events in 24,958 person-years follow-up (21 events per 1000 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 (Table 1). Only 3% of the women with no history of stones developed a stone 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 lower mean intake of fiber, fruit, 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 were each associated with a significant decreased risk of stone formation in women with no history of kidney stones (Table 2). In contrast, women with a 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 two quintiles of intake.

In multivariate analyses, women with no history of stones with the highest dietary fiber intake were 22% less likely (aHR 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 3). In a separate model, women with the highest fruit intake were 15% less likely (aHR 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 (aHR 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 prior to 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 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 towards 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 4-18% 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). Also, there was no significant interaction between fiber and fruit (p=0.92), fruit and vegetable (p=0.35) or fiber and vegetable (p=0.99) intake. In women with a history of stones prior to study participation, fiber, fruit, and vegetable intake were not associated (p=0.90, p=0.80, p=0.48, respectively) with a stone occurrence 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, fruit, 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 grams 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 from the traditional dietary risk factors including calories, fluid, sodium, animal protein and calcium intake. Increased intake of fruits and vegetables has previously been shown to increase urine volume, pH, potassium, magnesium, citrate, phytate and other stone inhibitors, resulting in a decrease in the supersaturation of calcium 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 were 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 are 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 are often incomplete, and thus patients may be globally reducing vegetable intake in an attempt to reduce their oxalate intake.[27] Reassuringly, this study specifically found 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 formed their first stone during this study and those who formed a recurrent stone during this study. Only 3% of women with no history of stones had an occurrence, compared to over 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 compared to 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 for 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. 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 food frequency questionnaire and **may be subject to recall bias and thus** 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 is 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, though self-reported stone events have previously been determined to be 97-98% accurate.[28, 29]

CONCLUSIONS

Higher intake of fruits, vegetables and fiber are 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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Role of the funding source

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Abbreviations

WHI	Women's Health Initiative
FFQ	food frequency questionnaire
BMI	body mass index
HR	hazards ratio
aHR	adjusted hazards ratio

95% CI 95% confidence intervals

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Table 1

Participant demographics for women with and without a history of kidney stones for postmenopausal women in the Women's Health Initiative Observational Study.

	No History of Nephrolithiasis n (%)	History of Nephrolithiasis n (%)	p value
	n= 80,451 (96.1%)	n= 3,471(3.9%)	
Demographics and History			
Age at enrollment (years)			0.001
50-59	25,801 (32.1)	1,060 (30.5)	
60-69	35,652 (44.3)	1,536 (44.3)	
≥70	18,998 (23.6)	875 (25.2)	
Mean±SD	63.5 ± 7.3	63.9 ± 7.3	0.005
Race/ethnicity			<0.001
White	78,584 (85.5)	2,953 (85.3)	
Black	5,663 (7.1)	204 (5.9)	
Hispanic	2,557 (3.2)	159 (4.6)	
Other	3,435 (4.3)	147 (4.2)	
Baseline history of diabetes mellitus	3,990 (5.0)	302 (8.7)	<0.001
Baseline supplemental calcium use	20,397 (25.4)	632 (18.2)	<0.001
Hormone therapy use			<0.001
Never	31,846 (39.6)	1,330 (38.4)	
Prior	11,897 (14.8)	570 (16.4)	
Current	36,635 (45.6)	1,567 (45.2)	
BMI (kg/m^2)			<0.001
<18.5 Underweight	938 (1.2)	40 (1.2)	
18.5-24.9 Normal weight	32,228 (40.5)	1,155 (33.6)	
25-29.9 Overweight	27,141 (34.1)	1,155 (33.6)	
30-34.9 Moderately obese	12,208 (15.3)	624 (18.2)	
≥35 Severely obese	7,062 (8.9)	459 (13.4)	
Mean±SD	27.1 ± 5.8	28.3 ± 6.2	<0.001
Geographical Region			0.02
Northeast	18,601 (23.1)	735 (21.2)	
South	20,305 (25.2)	942 (27.1)	
Midwest	18,114 (22.5)	770 (22.2)	
West	23,431 (29.1)	1,024 (29.5)	
Stone event during the study	2,390 (3.0)	547 (15.8)	<0.001
Study participation follow-up (years)			
Mean±SD	7.2 ± 1.1	7.2 ± 1.1	<0.001

		No History of Nephrolithiasis n (%)	History of Nephrolithiasis n (%)	p value
		n= 80,451 (96.1%)	n= 3,471(3.9%)	
Median (IQR 25^{th}-75^{th} percentile)		8 (7-8)	8 (7-8)	0.005
Dietary Intake				
Fiber intake (quintile)	Intake range (g/d)*			<0.001
Lowest	0-10.6	15,937 (19.8)	822 (23.7)	
Second	10.6-14.0	16,017 (19.9)	729 (21.0)	
Third	14.0-17.5	16,149 (20.1)	663 (19.1)	
Fourth	17.5-21.9	16,156 (20.1)	627 (18.1)	
Highest	21.9-99.4	16,192 (20.1)	630 (18.2)	
Mean±SD	16.6 ± 7.0	16.6 ± 7.0	16.0 ± 7.0	<0.001
Fruit intake (quintile)	(portions/day)*			<0.001
Lowest	0-1.0	16,109 (20.0)	899 (25.9)	
Second	1.0-1.5	15,821 (19.7)	706 (20.3)	
Third	1.5-2.1	16,527 (20.5)	699 (20.1)	
Fourth	2.1-3.0	15,868 (19.7)	568 (16.4)	
Highest	3.0-11	16,126 (20.0)	599 (17.3)	
Mean±SD	2.1 ± 1.3	2.1 ± 1.3	1.9 ± 1.3	<0.001
Vegetable intake (quintile)	(portions/day)*			<0.001
Lowest	0-1.2	16,016 (19.9)	815 (23.5)	
Second	1.2-1.7	15,984 (19.9)	696 (20.1)	
Third	1.7-2.4	16,136 (20.0)	691 (19.9)	
Fourth	2.4-3.3	16,119 (20.0)	647 (18.6)	
Highest	3.3-13.3	16,196 (20.1)	622 (17.9)	
Mean±SD	2.3 ± 1.3	2.3 ± 1.3	2.2 ± 1.3	<0.001

*The ranges of intake for the quintile categories of fiber, fruit and vegetable intake are non-overlapping ranges.

Table 2

Univariate odds of kidney stone formation in postmenopausal women during their participation in the Women's Health Initiative Observational Study, stratified by history of nephrolithiasis.

		No History of Nephrolithiasis n=80,451		History of Nephrolithiasis n=3,471	
Intake (quintile)	**Intake Range**	**HR (95% CI)**	**p value**	**HR (95% CI)**	**p value**
Fiber	(g/day)*		<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	(portions/day)*		<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	(portions/day)*		<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)	

*The ranges of intake for the quintile categories of fiber, fruit and vegetable intake are non-overlapping ranges.

Table 3

Association between fiber, fruit and vegetable intake and the risk of kidney stone formation during participation in the Women's Health Initiative Observational Study, in separate adjusted regression models stratified by history of nephrolithiasis.

		No History of Nephrolithiasis n=80,451		History of Nephrolithiasis n=3,471	
Intake (quintile)	**Intake Range**	**aHR[**] (95% CI)**	**p value**	**aHR[**] (95% CI)**	**p value**
Fiber	(g/day)[*]		<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	(portions/day)[*]		<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	(portions/day)[*]		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)	

[*] The ranges of intake for the quintile categories of fiber, fruit and vegetable intake are non-overlapping ranges.

[**] 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.