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Menopause and Risk of Kidney Stones

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Abstract

Purpose: Metabolic changes due to menopause may alter urine composition and kidney stone risk but results of prior work on this association have been mixed. We examined menopause and the risk of incident kidney stones, and changes in 24-hour urine composition in the NHS (Nurses' Health Study) II.

Materials and Methods: Using multivariate adjusted Cox proportional hazards models we prospectively analyzed 108,639 NHS II participants who provided information on menopause and kidney stones. We also analyzed 24-hour urine collections from 658 participants who performed a collection while premenopausal and a repeat collection after menopause.

Results: During 22 years of followup there were 3,456 incident kidney stones. The multivariate adjusted relative risk of an incident kidney stone in post-menopausal participants compared with premenopause was 1.27 (95% CI 1.08−1.46). On stratified analysis compared with premenopause the multivariate adjusted relative risk of natural and surgically induced menopause was 1.27 (95% CI 1.09−1.48) and 1.43 (95% CI 1.19−1.73), respectively. Among the 74,505 postmenopausal participants there was a total of 1,041 incident stone events. Compared with no hormone therapy neither current nor past use was significantly associated with kidney stone risk. Compared with premenopause the postmenopausal urine collections had lower mean calcium, citrate, phosphorus and uric acid, and higher mean volume.

Conclusions: Postmenopausal status is associated with a higher risk of incident kidney stones. Natural menopause and surgical menopause are independently associated with higher risk. There are small but significant differences in urine composition between premenopausal and postmenopausal urine collections.

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Kidney; Nephrolithiasis; Premenopause; Postmenopause; risk

MENOPAUSE may be associated with kidney stones because of the changes in bone metabolism at menopause.[1] It is unclear whether there is a change in the kidney stone risk with menopause as prior work on this association has shown mixed results. For example, a previous NHS I study revealed no association between natural menopause and incident kidney stones but the risk was 39% higher in participants with surgical menopause.[2] The same NHS I study showed no association between postmenopausal hormone therapy use and kidney stones. However, in the WHI there was a 21% higher risk of kidney stones in the group of women randomized to hormone therapy even several years after menopause and on secondary analysis excluding participants who had stopped hormone therapy this risk was 38% higher in the hormone therapy group.[3] Yet in a cross-sectional study of 24-hour urine composition in postmenopausal women those treated with estrogen had lower urinary calcium and calcium oxalate supersaturation than women not receiving estrogen.[4]

Furthermore, despite the importance of 24-hour urine collection in kidney stone evaluation and management to our knowledge no previous study has examined changes in the composition of the 24-hour collection from premenopause to postmenopause in the same individuals.

Due to the inconsistencies in the literature related to menopause and kidney stone risk, and the lack of studies on changes in 24-hour urine composition after menopause we performed 2 prospective studies in the NHS II cohort. We examined the association between menopause and incident kidney stones, and we compared changes in 24-hour urine composition from premenopause to postmenopause.

METHODS

Study Population

The NHS II is an ongoing cohort that began in 1989 when 116,430 female registered nurses 25 to 42 years old answered the baseline questionnaire. Every 2 years this cohort is followed with questionnaires that update lifestyle and disease information. Cohort followup is more than 90% of eligible person-time. Individuals with a baseline history of kidney stones were excluded from analyses.

Menopausal Status and Postmenopausal Hormone Therapy Assessment

On the initial 1989 questionnaire participants were asked about menopausal status, age at menopause, the reason for menopause (ie natural, surgery or radiation) and the use of postmenopausal hormone therapy. This information was updated every 2 years. Self-reports of the type of menopause and age at menopause were previously validated in a similar cohort.[5]

Kidney Stone Ascertainment

Participants reported a diagnosis of an incident kidney stone on the biennial questionnaires. Self-reported incident kidney stones were confirmed by supplemental questionnaire requesting information such as the date of diagnosis and symptoms. A validation study performed in NHS II of 858 women confirmed 98% of self-reports compared with medical records.[6] In the validation study of those with a stone composition report 79% of study participants had a stone composed of at least 50% calcium oxalate.[6]

24-Hour Urine Collections

Participants completed 2, 24-hour urine collections. The first collection was performed when the participant was premenopausal and the second was performed after menopause.

Premenopausal 24-hour urine collections were collected from 201 of the total of 658 participants from 1994 and 2007. Half of the participants who were invited to participate in this collection had a history of kidney stone disease. Participants were excluded from analysis if they had a history of cancer other than nonmelanoma skin cancer or cardiovascular disease.[7,8] Urine collections of these participants were performed using the Mission® Pharmacal system. The remaining 457 participants completed the premenopausal 24-hour urine collection in 2010 to 2011 using the Litholink system (LabCorp, Burlington, North Carolina).

Participants excluded from urine collection had a history of cancer other than nonmelanoma skin cancer or a history of hypertension prior to the invitation to participate. Participants with a previously reported history of hypertension on a biennial questionnaire were not invited to participate in the 24-hour urine collection project because the collection was initially done as part of a study examining urinary risk factors for incident hypertension.

All postmenopausal urine collections were performed in 2015 by 658 participants using the Litholink system. The inclusion criterion for the postmenopausal collection was the completion of a premenopausal urine collection.

Assessments

Diet.—Semiquantitative food frequency questionnaires were used every 4 years from 1991 to 2013 to assess the average dietary intake of more than 130 food items and more than 20 beverages during the previous year. The validity and reproducibility of the food frequency questionnaires were previously reported.[9] Nutrient variables were energy adjusted to reflect the nutrient composition of the diet independent of the total food consumed. Supplemental calcium and vitamin D intake was determined by frequency, amount of use, and supplement brand and type.

Nondietary Covariates.—Age, weight and height were queried on the 1989 questionnaire, and age and weight were updated on all followup questionnaires. The validity of self-reported weight was reported in 2 similar cohorts.[10] Validation of the self-report of hypertension and diabetes was documented and this information was updated every 2 years.[11–13] Medication use was updated every 2 years.

Prospective Statistical Analyses

Incident Kidney Stones.—We used multivariate Cox proportional hazards regression models to estimate age and the MVRR of an incident kidney stone among postmenopausal women compared with premenopausal women. A separate analysis was stratified by the reason for menopause. On an analysis limited to post-menopausal women we compared postmenopausal hormone therapy use with no hormone therapy. Variables included in the multivariate models were age (continuous), BMI, race, calcium supplement use (none, or 0 to 100, 101 to 500 or greater than 500 mg per day), thiazide use, history of hypertension, history of diabetes mellitus, time since menopause (0 to 4 years, more than 4 to 8, more than 8 to 12 and more than 12) and quintiles of the intake of fluid, dietary calcium, animal protein, sodium, potassium, magnesium, oxalate, vitamins C and D, and alcohol intake (6 categories). Nondietary variables were updated in the model every 2 years and dietary variables were updated every 4 years.

Analyses were done with SAS®, version 9.4. The study research protocol was approved by the Brigham and Women's Hospital institutional review board.

24-Hour Urine Collections.—Participants with 24-hour creatinine in the top or bottom 1% were excluded from study to remove collections that were possibly over or under collections. The paired t-test was used to compare differences between individual urine factors. Multivariate linear regression was applied to examine predictors of difference in 24-hour urine calcium for postmenopausal vs premenopausal urine. A secondary multivariate logistic regression analysis was done to examine predictors of an absolute change of 100 mg per day or greater of urinary calcium. Additional analyses were similarly performed to examine differences in 24-hour oxalate, citrate, phosphorus, pH and uric acid in premenopausal vs postmenopausal urine collections.

All models were adjusted for age (continuous), BMI (continuous), race, thiazide use, dietary calcium (continuous), supplemental calcium (continuous), total vitamin D (continuous), low bone density (yes/no), hormone therapy use (current, past or unknown), age at menopause, family history of kidney stones and difference in the 24-hour urine excretion of urinary factors as appropriate (ie creatinine, calcium, sodium and citrate magnesium continuous and considered as postmenopause minus premenopause). Participants with any missing data on covariates were excluded from study.

RESULTS

Incident Kidney Stones

The prospective analysis of incident kidney stone formation was done in 108,639 participants with a total of 1,862,434 person-years of followup. Supplementary table 1 (http://jurology.com/) lists participant characteristics by menopausal status. Postmenopausal participants were older, more likely to have a higher BMI, more likely to be on a thiazide and more likely to have hypertension and diabetes. During 22 years of followup a symptomatic incident kidney stone developed in 3,456 participants.

Postmenopausal status was independently associated with a higher risk of an incident kidney stone. In postmenopausal vs premenopausal participants the MVRR was 1.27 (95% CI 1.08–1.46, table 1). On analysis stratified by menopause type the MVRRs of natural and surgically induced menopause were 1.27 (95% CI 1.09–1.48) and 1.43 (95% CI 1.19–1.73), respectively, compared with before menopause (table 2).

Among 74,505 postmenopausal participants there was a total of 1,041 incident stone events. Receipt of postmenopausal hormone therapy was not significantly associated with the risk of kidney stones in current and past users (MVRR 1.11, 95% CI 0.94–1.30 and 1.06, 95% CI 0.90–1.26, respectively) compared with no postmenopausal hormone therapy (supplementary table 2, http://jurology.com/). Time since menopause was not independently associated with the risk of kidney stones.

24-Hour Urine Collections

After exclusions there were 658 participants who performed premenopausal and postmenopausal 24-hour urine collections. Supplementary table 3 (http://jurology.com/) shows the characteristics of those patients, of whom 143 (22%) had a history of kidney stones. Compared with premenopausal participants hypertension and diabetes had developed in more postmenopausal participants, and there was a higher intake of calcium and vitamin D supplementation.

Compared with the premenopausal collection the postmenopausal collection showed lower mean urinary calcium (–17 mg per day, 95% CI –24—10, supplementary table 3, http://jurology.com/). On analysis stratified by kidney stone history there was no substantial difference in results between individuals with vs without kidney stones. In the multivariate model the only factors associated with the difference in urinary calcium between the 2 collections were thiazide use (−44 mg per day, 95% CI −69−−19) and BMI (−1 mg per day per kg/m^2, 95% CI −3−−0.2, table 3).

No factors were associated with large changes of 100 mg per day or greater in urinary calcium. In a multivariate model using only postmenopausal collections there was no difference in urinary calcium based on current or past hormone therapy compared with no hormone therapy. For other urinary factors compared with premenopausal status the post-menopausal urine collection showed lower mean citrate (mean difference e43 mg per day, 95% CI −63−−25), phosphorus (mean difference −79 mg per day, 95% CI −101−−58) and uric acid (mean difference −33 mg per day, 95% CI −43−−22), higher mean urine volume (mean difference 0.13 l per day, 95% CI 0.07−0.18) and no difference in mean oxalate or pH (supplementary table 3, http://jurology.com/). On separate analyses there was no significant predictor of differences between premenopausal and postmenopausal urine volume, pH and urine excretion of oxalate, phosphorus, citrate and uric acid (supplementary table 4, http://jurology.com/).

DISCUSSION

In this prospective analysis we found that post-menopausal status was associated with a higher risk of an incident kidney stone. Natural menopause and surgical menopause were

independently associated with higher risk. We found small differences in urine composition between premenopausal and postmenopausal 24-hour urine collections.

In contrast to our current findings, a prior study in the distinct NHS I cohort did not show that natural menopause was associated with incident kidney stones (MVRR 1.12, 95% CI 0.89e1.41).[2] The differences in findings may be because this NHS II study represents longer followup and more cases than the previous study (747 vs 3,456). Each study adjusted for BMI and differences in dietary intake. Thus, differences in these well established kidney stone risk factors would not explain the difference in results.

A prior study in the WHI demonstrated that among postmenopausal women estrogen therapy was associated with a 21% higher risk of kidney stones.[3] In our study a secondary analysis limited to postmenopausal women indicated no independent association between hormone therapy use and kidney stones. Our age adjusted model showed a result similar to the WHI series. However, in our final multivariate model the association was no longer significant.

In the WHI study participants were randomized to the hormone therapy group[3] but NHS II is an observational study. In our cohort hormone use was determined by the participant and the physician, and administration was initiated in the perimenopausal period. There are other differences between the WHI and NHS II cohorts, including a higher kidney stone rate in the WHI cohort compared with the NHS II cohort. This may be attributable to differences in kidney stone diagnosis ascertainment since the WHI uses self-report of kidney stone alone while the NHS II confirms self-reported cases.

To our knowledge this is the first study to evaluate the composition of 24-hour urine collection in the same participants at premenopausal and post-menopausal time points. In a retrospective analysis of hormone therapy in 89 postmenopausal women the 39 on estrogen therapy had lower urinary calcium excretion (mean±SD 155±62 vs 193±90 mg per day, p <0.02).[4] In our prospective study of 24-hour urine collections hormone therapy was not a predictor of change in the postmenopausal collection of any urinary factor, including calcium, phosphorus, pH, citrate or uric acid. Our results may differ from these prior results because our study was prospective and we assessed the same women at premenopausal and postmenopausal time points. In addition, in previous studies spot or 24-hour urine collections were used and we used 24-hour collections. Among the studies there were also differences in the time from menopause to hormone therapy initiation as well as hormone therapy initiation to urine collection.

The mechanism of the higher risk of kidney stones among postmenopausal women remains unclear. There were statistically significant differences between premenopausal and postmenopausal urine compositions. However, several of these differences were in the opposite expected direction for higher stone risk at the postmenopausal time point, such as lower calcium, phosphorus and uric acid, and higher urine volume.

It may be that the risk of kidney stones changes with time after menopause. To address this we included time since menopause variables in our models for the 24-hour urine collection and for incident kidney stones. We could not look at changes less than 2 years after menopause but we noted no difference in kidney stone risk or urinary calcium based on time

since menopause. Another consideration is that our study had limited ability to examine the supersaturation of calcium oxalate, calcium phosphate or uric acid as different methods of calculating supersaturation are used at the Litholink and Mission Pharmacal laboratories. However, we examined the main contributors to supersaturation, ie calcium, oxalate, urine volume and citrate for calcium oxalate. It is possible that there is an unmeasured inhibitor or promotor in urine related to menopause.

Our study has limitations. The observational design did not remove the possibility of residual confounding. For urine collections there were only 1 premenopausal collection and 1 postmenopausal collection. We also did not have data on kidney function in study participants or on the use of uric acid lowering drugs or supplemental alkali. In our analysis of hormone therapy participants were not randomized to hormone use but we adjusted for potential confounders. We did not have stone composition reports for the majority of stone formers in our incident kidney stone analysis but in our validation study most stones were calcium oxalate.[6] Finally, the cohort was pre-dominantly white and, thus, generalizability may be limited.

CONCLUSIONS

Natural menopause and surgical menopause were associated with a higher risk of an incident kidney stone. There were small but statistically significant differences in urine composition since the postmenopausal collections showed lower mean calcium, citrate, phosphorus and uric acid, and higher mean volume than the premenopausal collections.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Abbreviations and Acronyms

BMI	body mass index
MVRR	multivariate adjusted relative risk
NHS	Nurses’ Health Study
WHI	Women’s Health Initiative

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Table 1

Age and multivariate adjusted relative risks for incident kidney stones by menopausal status (1991–2013)

	Pre-menopause	Post-menopause	p-value
Cases	2,415	1,041	
Person-years	1,304,561	557,873	
Age-adjusted RR	1.0 (ref)	1.30 (1.17, 1.44)	<0.001
MV-adjusted RR	1.0 (ref)	1.27 (1.08 to 1.46)	0.003

Multivariate Model: Adjusted for age, body mass index, race, dietary factors (calcium, magnesium, potassium, sodium, animal protein, oxalate, vitamin D, vitamin C, alcohol, total fluid), supplemental calcium intake, thiazide, history of hypertension, history of diabetes mellitus, post-menopausal hormone therapy

*Abbreviations: MV, multivariate; RR, relative risk

Table 2

Age and multivariate adjusted relative risks for incident kidney stones by type of menopause (1991–2013)

	Pre-menopause	Post-Menopause, Natural	Post-menopause, Surgical
Cases	2,415	577	425
Person-years	1,304,561	347,252	184,207
Age-adjusted RR	1.0 (ref)	1.12 (0.97, 1.28)	1.51 (1.34 to 1.71)
MV-adjusted RR	1.0 (ref)	1.27 (1.09 to 1.48)	1.43 (1.19 to 1.73)

Multivariate Model: Adjusted for age, body mass index, race, dietary factors (calcium, magnesium, potassium, sodium, animal protein, oxalate, vitamin D, vitamin C, alcohol, total fluid), supplemental calcium intake, thiazide, history of hypertension, history of diabetes mellitus, post-menopausal hormone therapy

*Abbreviations: MV, multivariate; RR, relative risk

**Type of menopause for remaining 39 cases was radiation induced menopause

Table 3

Multivariate model for difference in post-minus pre-menopausal urinary calcium excretion (N=658)

Variable	Calcium difference (mg/day)	95 % Confidence interval	p-value
Age, years	0.9	−2 to 3	0.47
Body mass index kg/m^2	−1	−3 to −0.2	0.02
Family history of kidney stones	−1	−16 to 13	0.85
Thiazide use	−44	−69 to −19	<0.001
Calcium supplements per 100 mg/d	−0.3	−2 to 1	0.62
Vitamin D supplements per 100 IU/d	0.04	−0.8 to 1	0.93
Dietary calcium per 100 mg/d	0.3	−1 to 2	0.70
Low bone density	−7	−26 to 13	0.51
Age at menopause	−1	−3 to 1	0.17
Current hormone use	7	−10 to 23	0.43

*The above model also adjusted for difference in post-minus pre-menopause for other urinary variables (sodium, magnesium, citrate, and creatinine)

**Body mass index, age, thiazide use, dietary calcium intake, supplemental calcium intake, supplemental vitamin D intake and low bone density diagnosis based on post-menopausal time point