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Diabetes mellitus and the risk of nephrolithiasis

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Background. Insulin resistance is a central feature of type 2 diabetes mellitus (DM) and may increase the risk of kidney stone formation. Existing cross-sectional data on the association between DM and nephrolithiasis are limited, and no prospective study to date has evaluated the relation between DM and the risk of kidney stones.

Methods. To evaluate the relation between DM and prevalent kidney stones, we conducted a cross-sectional study of 3 large cohorts including over 200,000 participants: the Nurses' Health Study I (older women), the Nurses' Health Study II (younger women), and the Health Professionals Follow-up Study (men). We then prospectively studied the association between DM and incident nephrolithiasis over a combined 44 years of follow-up. Because insulin resistance can precede the diagnosis of DM by decades, we also prospectively examined the relation between kidney stones and the diagnosis of incident DM. Multivariate regression models adjusted for age, body mass index, thiazide diuretic use, fluid intake, and dietary factors.

Results. At baseline, the multivariate relative risk of prevalent stone disease in individuals with DM compared to individuals without was 1.38 (95% CI 1.06-1.79) in older women, 1.67 (95% CI 1.28-2.20) in younger women, and 1.31 (95% CI 1.11-1.54) in men. Prospectively, the multivariate relative risk of incident kidney stone formation in participants with DM compared to participants without was 1.29 (95% CI 1.05-1.58) in older women, 1.60 (95% CI 1.16-2.21) in younger women, and 0.81 (95% CI 0.59-1.09) in men. The multivariate relative risk of incident DM in participants with a history of kidney stones compared to participants without was 1.33 (95% CI 1.18-1.50) in older women, 1.48 (95% CI 1.14-1.91) in younger women, and 1.49 (95% CI 1.29-1.72) in men.

Conclusion. DM is a risk factor for the development of kidney stones. Additional studies are needed to determine if the increased risk of DM in stone formers is due to subclinical insulin resistance.

Nephrolithiasis is a major cause of morbidity. Approximately 10% of men and 5% of women will experience a symptomatic kidney stone by the age of 75 years [1–3], and more than $2 billion is spent annually on the treatment of stone disease [4, 5]. The identification of common systemic diseases that increase the risk of kidney stone formation may help in the prevention of incident and recurrent stones.

Type 2 diabetes mellitus is characterized by insulin resistance [6], a metabolic derangement that may increase the risk of kidney stone formation. Metabolic trials have demonstrated that insulin resistance is associated with defects in renal ammonium production [7, 8], and stone formers with diabetes may have more acidic urine than stone formers without diabetes [9]. Although a low urinary pH plays a major role in the formation of uric acid kidney stones [10, 11], a defect in renal acid excretion also could lead to hypocitraturia, an important risk factor for calcium stones [12, 13]. In addition, the compensatory hyperinsulinemia of insulin resistance [6] may increase the urinary excretion of calcium [14–16].

Despite the compelling effect of insulin resistance on urine composition, data on the potential association between diabetes and nephrolithiasis are sparse. One cross-sectional study indicated that the prevalence of stone disease in subjects with diabetes was 21%, compared to 8% in nondiabetic controls [17]. However, this study did not adjust for body mass index, an important risk factor for both diabetes and nephrolithiasis [18]. The results of another cross-sectional study were inconclusive [19]. To date, no prospective study has evaluated the association between diabetes mellitus and the risk of kidney stones.

To determine if diabetes mellitus was associated with prevalent kidney stones, we performed cross-sectional analyses in 3 large cohorts: the Nurses' Health Studies I and II (NHS I and NHS II) and the Health Professionals Follow-up Study (HPFS). We then prospectively studied each cohort to examine the relation between diabetes mellitus and incident nephrolithiasis. Because insulin

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resistance and compensatory hyperinsulinemia can precede the diagnosis of type 2 diabetes by decades [6], we also evaluated kidney stones as a potential risk factor for the diagnosis of incident diabetes.

METHODS

Study population

Nurses' Health Study (NHS I). In 1976, 121,700 female registered nurses between the ages of 30 and 55 years completed and returned an initial questionnaire that provided detailed information on medical history, lifestyle, and medications. This cohort, like NHS II and HPFS, is followed by biennial mailed questionnaires, which include inquiries about the incidence of newly diagnosed diseases, including diabetes and kidney stones. Because we first asked NHS I participants about kidney stones in 1992, the current analysis was limited to women who answered questionnaires in 1992 or later. For this study, we started follow-up in 1980 because before that date we lacked information on diet.

Nurses' Health Study II (NHS II). In 1989, 116,671 female registered nurses between the age of 25 and 42 years enrolled in NHS II by completing and returning an initial questionnaire. Dietary information was first collected from this cohort in 1991.

Health Professionals Follow-up Study (HPFS). In 1986, 51,529 male dentists, optometrists, osteopaths, pharmacists, podiatrists, and veterinarians between the ages of 40 and 75 years enrolled in HPFS by completing and returning an initial questionnaire.

Ascertainment of diabetes mellitus

All participants who reported a diagnosis of diabetes mellitus on a biennial questionnaire were sent a supplementary questionnaire about symptoms, diagnostic tests, and hypoglycemic therapy. Before 1996, a reported case of diabetes mellitus was considered confirmed if at least 1 of the following was reported: (*1*) at least 1 typical symptom (weight loss, hunger, excessive thirst, or polyuria) and a fasting plasma glucose of at least 140 mg/dL or a random plasma glucose of at least 200 mg/dL; (*2*) at least 2 elevated plasma glucose levels (fasting $\geq$140 mg/dL; random, $\geq$200 mg/dL; and/or a concentration $\geq$200 mg/dL after $\geq$2 hours on glucose tolerance testing) on different occasions without symptoms; or (*3*) treatment with a hypoglycemic medication (insulin or oral agents). Subjects with confirmed diabetes mellitus who began taking insulin within 1 year of diagnosis and who reported a history of ketoacidosis or ketonuria on at least 2 occasions were considered to have type 1 diabetes mellitus. The fasting glucose level for diagnosis was changed to 126 mg/dL in June 1996, and this lower threshold was used to define cases after 1996. The criteria for the classification of diabetes mellitus in the Nurses' Health Study have been published in detail previously [20].

In a sample of NHS I and HPFS participants, 98% and 97% of the self-reported diabetes cases documented by the supplementary questionnaire were confirmed by medical record review [20, 21].

Ascertainment of kidney stones

The primary outcome was an incident kidney stone accompanied by pain or hematuria. The subjects reported on the interval diagnosis of kidney stones every 2 years. Any study participant who reported a new kidney stone was sent an additional questionnaire to determine the date of occurrence and the symptoms from the stone. We confirmed the validity of the self-reported incident stones in HPFS by obtaining medical records from 232 men in the cohort; chart review confirmed 95% of the cases. We also examined medical records from 194 women in NHS I and 237 women in NHS II who reported incident kidney stones. The records confirmed the diagnosis for 96% of the cases in NHS I and 98% of the cases in NHS II.

Ascertainment of diet

The semiquantitative food-frequency questionnaire (first mailed to the HPFS in 1986, to the NHS I in 1980, and to the NHS II in 1991) asked about the average use of more than 130 foods and beverages during the previous year. In addition, respondents provided information on the use of nutritional supplements, taken either alone or in multivitamin form. Subsequently, a version of this food-frequency questionnaire (FFQ) has been mailed to study participants every 4 years. The reproducibility and validity of the FFQs in the HPFS and NHS I have been documented [22, 23].

Nutrient intake was computed from the reported frequency of consumption of each specified unit of food and from USDA data on the content of the relevant nutrient in specified portions. Nutrient values were adjusted for total caloric intake to determine the composition of the diet independent of the total amount of food eaten [24, 25].

The intake of supplemental calcium in multivitamin or isolated form was determined by the brand, type, and frequency of reported use.

Ascertainment of nondietary covariates

Information on age, weight, and height was obtained on the baseline questionnaire. Self-reported weight was updated every 2 years. Body mass index (BMI) was calculated as the weight in kilograms divided by the square of height in meters. Self-reported weight has been validated in HPFS and NHS I [26].

In HPFS and NHS II, thiazide diuretic use was updated every 2 years. In NHS I, thiazide use was determined in 1980, 1982, and then every 6 years until 1994, when biennial updates started. Information on hypertension was obtained at baseline and then every 2 years. The validity of self-reported hypertension has been documented [27].

Statistical analysis

Cross-sectional analyses. The cross-sectional analyses assessed the prevalence of kidney stones according to the presence or absence of a diagnosis of diabetes at baseline (1980 for NHS I, 1991 for NHS II, and 1986 for HPFS). Categorical variables were compared using the chi-square test and continuous variables were compared using analysis of variance (ANOVA). Logistic regression was used to control for the following baseline covariates simultaneously: age (continuous), BMI (continuous), alcohol intake (7 categories), the use of thiazide diuretics (yes or no), supplemental calcium use (4 categories), and the intake of fluid, sucrose, potassium, sodium, animal protein, magnesium, phytate, and dietary calcium (quintile groups).

Prospective analyses. For each cohort, we performed 2 prospective analyses. The first analysis evaluated diabetes mellitus (updated every 2 years) as a risk factor for incident symptomatic kidney stone formation. Subjects reporting a kidney stone at baseline were excluded at the start of the study. The second prospective analysis evaluated a history of kidney stones (updated every 2 years) as a risk factor for the development of incident type 2 diabetes. Participants reporting diabetes at baseline were excluded at the start of the study.

For the NHS I, person-months of follow-up were counted from the date of the return of the 1980 questionnaire to the date of an incident case (a kidney stone for the first analysis, and type 2 diabetes for the second analysis) or death or to May 31, 2000. For the NHS II, person-months of follow-up were counted from the date of the return of the 1991 questionnaire to the date of an incident case or death or to May 31, 2001. For the first prospective analysis of HPFS, 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 to January 31, 2000. Because we have only confirmed incident cases of type 2 diabetes in men through 1998, the second prospective analysis of HPFS counted person-months of follow-up from baseline to the date of diagnosis of diabetes or death or to January 31, 1998. We allocated person-months of follow-up according to exposure status at the start of each 2-year follow-up period.

Cox proportional hazards regression was used to adjust for potential confounding in the prospective analyses. The covariates included in the multivariate Cox models were the same as for the logistic regression analyses, but were updated throughout the study. Each dietary exposure was updated every 4 years. If complete information on diet was missing at the start of a time period, the subject was excluded for that time period.

We calculated 95% confidence intervals for all relative risks. All P values are 2-tailed. All data were analyzed by using SAS software, version 8.2 (SAS Institute, Inc., Cary, NC, USA). The research protocol for this study was reviewed and approved by the institutional review board of Brigham and Women's Hospital.

Table 1. Baseline characteristics of older women (NHS I), younger women (NHS II), and men (HPFS) by diabetes mellitus[a]

	Diabetes +	Diabetes −	P value
NHS I			
Number %	1473 (1.9%)	74,266 (98.1%)	
Age *years*[b]	48.6	46.3	<0.001
BMI kg/m^2[b]	28.1	24.3	<0.001
Current thiazide use	329 (22.3%)	7382 (9.9%)	<0.001
Kidney stone history	64 (4.3%)	2029 (2.7%)	<0.001
NHS II			
Number %	949 (1.0%)	94,485 (99.0%)	
Age *years*[b]	37.6	36.1	<0.001
BMI kg/m^2 [b]	29.0	24.6	<0.001
Current thiazide use	73 (7.7%)	1683 (1.8%)	<0.001
Kidney stone history	58 (6.1%)	3093 (3.3%)	<0.001
HPFS			
Number %	1568 (3.2%)	47,737 (96.8%)	
Age *years*[b]	60.9	54.4	<0.001
BMI kg/m^2 [b]	26.4	25.5	<0.001
Current thiazide use	317 (20.2%)	4420 (9.3%)	<0.001
Kidney stone history	177 (11.3%)	4002 (8.4%)	<0.001

[a]1980 for NHS I, 1991 for NHS II, and 1986 for HPFS.
[b]Values expressed as means.

RESULTS

Cross-sectional analyses

At the beginning of the study, 75,739 older women (NHS I), 95,434 younger women (NHS II), and 49,305 men (HPFS) provided complete information on diabetes mellitus, kidney stone disease, and diet. At baseline, 1473 older women (1.9%), 949 younger women (1.0%), and 1568 men (3.2%) reported a history of diabetes mellitus. The characteristics of the study participants by history of reported diabetes mellitus are shown in Table 1. Participants with diabetes mellitus were older ($P < 0.001$), had a higher BMI ($P < 0.001$), were more likely to use thiazide diuretics ($P < 0.001$), and were more likely to report a history of kidney stones ($P < 0.001$).

A history of diabetes mellitus was independently associated with a history of nephrolithiasis in all 3 cohorts (Table 2). The multivariate relative risk of prevalent kidney stones in participants with diabetes mellitus compared to participants without was 1.38 (95% CI 1.06-1.79) in older women, 1.67 (95% CI 1.28-2.20) in younger women, and 1.31 (95% CI 1.11-1.54) in men. Further

Table 2. Baseline relative risk of prevalent nephrolithiasis according to diabetes history in older women (NHS I), younger women (NHS II), and men (HPFS)[a]

	Age-adjusted RR	Multivariate RR[b]
NHS I		
Diabetes –	1.00 (reference)	1.00 (reference)
Diabetes +	1.55 (1.20, 1.99)	1.38 (1.06, 1.79)
NHS II		
Diabetes –	1.00 (reference)	1.00 (reference)
Diabetes +	1.84 (1.41, 2.41)	1.67 (1.28, 2.20)
HPFS		
Diabetes –	1.00 (reference)	1.00 (reference)
Diabetes +	1.21 (1.03, 1.42)	1.31 (1.11, 1.54)

[a]1980 for NHS I, 1991 for NHS II, and 1986 for HPFS.
[b]Relative risks (RR) include 95% confidence intervals in parentheses. The multivariate model includes age, body mass index, use of thiazide diuretics (yes or no), fluid intake (in quintiles), alcohol use (7 categories), calcium supplement use (4 categories), and dietary intake of calcium, animal protein, potassium, sodium, phytate, magnesium, and sucrose (all in quintiles).

Table 3. Relative risk of incident symptomatic kidney stones according to diabetes history in older women (NHS I), younger women (NHS II), and men (HPFS)[a]

	Person-years	Kidney stones	Age-adjusted RR	Multivariate RR[b]
NHS I				
Diabetes –	1,371,080	1578	1.00 (reference)	1.00 (reference)
Diabetes +	65,566	109	1.45 (1.20, 1.77)	1.29 (1.05, 1.58)
NHS II				
Diabetes –	824,076	1491	1.00 (reference)	1.00 (reference)
Diabetes +	12,291	40	1.86 (1.36, 2.56)	1.60 (1.16, 2.21)
HPFS				
Diabetes –	450,984	1426	1.00 (reference)	1.00 (reference)
Diabetes +	21,676	44	0.76 (0.56, 1.03)	0.81 (0.59, 1.09)

[a]Subjects who reported kidney stones on the baseline questionnaire were excluded.
[b]Relative risks (RR) include 95% confidence intervals in parentheses. The multivariate model includes age, body mass index, use of thiazide diuretics (yes or no), fluid intake (in quintiles), alcohol use (7 categories), calcium supplement use (4 categories), and dietary intake of calcium, animal protein, potassium, sodium, phytate, magnesium, and sucrose (all in quintiles).

adjustment for hypertension did not materially change the results.

Prospective analyses

Incident kidney stone formation according to diabetes history. After excluding participants who reported a history of kidney stones at baseline, we prospectively studied 93,758 older women (NHS I), 101,877 younger women (NHS II), and 46,062 men (HPFS). Over the course of the study, we documented a total of 4688 incident kidney stones (1687 in NHS I, 1531 in NHS II, and 1470 in HPFS).

A self-reported history of diabetes mellitus was independently associated with an increased risk of incident nephrolithiasis in women, but not men (Table 3). The multivariate relative risk of kidney stone formation in participants with self-reported diabetes mellitus compared to participants without was 1.29 (95% CI 1.05-1.58) in older women, 1.60 (95% CI 1.16-2.21) in younger women, and 0.81 (95% CI 0.59-1.09) in men. Excluding participants with diabetes mellitus at baseline (i.e., restricting the analyses to confirmed cases of incident type 2 diabetes mellitus) and further adjustment for hypertension did not materially change the results.

Incident diabetes according to kidney stone history. After excluding participants who reported a history of diabetes at baseline, we prospectively studied 94,448 older women (NHS I), 104,911 younger women (NHS II), and 49,101 men (HPFS). Over the course of the study, we documented a total of 6460 incident cases of type 2 diabetes (4300 in NHS I, 785 in NHS II, and 1375 in HPFS).

A self-reported history of kidney stones was independently associated with an increased risk of incident diabetes in women and men (Table 4). The multivariate relative risk of diabetes in participants with self-reported kidney stones compared to participants without was 1.33 (95% CI 1.18-1.50) in older women, 1.48 (95% CI 1.14-1.91) in younger women, and 1.49 (95% CI 1.29-1.72) in men. Excluding participants with kidney stones at baseline did not materially change the results.

Table 4. Relative risk of incident type 2 diabetes according to kidney stone history in older women (NHS I), younger women (NHS II), and men (HPFS)[a]

	Person-years	Diabetes	Age-adjusted RR	Multivariate RR[b]
NHS I				
Stones –	1,522,293	4005	1.00 (reference)	1.00 (reference)
Stones +	64,590	295	1.65 (1.47, 1.86)	1.33 (1.18, 1.50)
NHS II				
Stones –	988,262	712	1.00 (reference)	1.00 (reference)
Stones +	44,290	73	2.26 (1.78, 2.88)	1.48 (1.14, 1.91)
HPFS				
Stones –	399,935	1157	1.00 (reference)	1.00 (reference)
Stones +	44,373	218	1.54 (1.33, 1.78)	1.49 (1.29, 1.72)

[a]Subjects who reported diabetes on the baseline questionnaire were excluded.
[b]Relative risks (RR) include 95% confidence intervals in parentheses. The multivariate model includes age, body mass index, use of thiazide diuretics (yes or no), fluid intake (in quintiles), alcohol use (7 categories), calcium supplement use (4 categories), and dietary intake of calcium, animal protein, potassium, sodium, phytate, magnesium, and sucrose (all in quintiles).

DISCUSSION

Our study found that diabetes mellitus was positively associated with nephrolithiasis, independent of age, BMI, thiazide diuretic use, and diet. Diabetes was associated with prevalent stone disease in all 3 cohorts, and was associated with an increased risk of incident kidney stone

formation in older and younger women. In addition, a history of kidney stones was associated with an increased risk of incident type 2 diabetes in men and women.

Diabetes may increase the risk of kidney stone formation by altering the composition of the urine. Insulin resistance, a central feature of type 2 diabetes, may manifest in the kidney as a defect in ammonium production [7, 8]. Insulin resistance is associated with high levels of plasma free fatty acids, which can enter the proximal tubule cells and interfere with the utilization of glutamine in the production of ammonium [28–30]. In addition, insulin resistance at the level of the kidney may directly affect ammoniagenesis. In vitro studies demonstrate that insulin stimulates renal ammonium production from the substrate L-glutamine [31, 32]. Insulin may also play a role in the function of the proximal renal tubule Na^+/H^+ exchanger that is needed for either direct transport or ionic trapping of ammonium in the tubular lumen [33].

In vivo data in humans have confirmed that insulin plays an important role in renal acidification by increasing the production of ammonium, and that insulin resistance is associated with an impaired ability to excrete an acid load [7, 8]. In a recent metabolic trial, 13 patients with a history of recurrent uric acid nephrolithiasis and 55 healthy volunteers underwent hyperinsulinemic euglycemic clamp [8]. In the healthy volunteers, insulin levels increased from a mean of 14 microunits/mL at baseline to 173 microunits/mL during the last 40 minutes of insulin infusion [8]. The levels of urinary ammonium in these subjects during this time frame increased by 48%, and urinary pH increased from a mean of 6.1 to 6.8 [8]. Of note, lower glucose disposal rate (i.e., greater insulin resistance) correlated significantly with lower urinary pH ($P = 0.01$) in all subjects [8].

Other clinical data indirectly support the results of this metabolic trial. For instance, stone formers with diabetes may have more acidic urine than stone formers without diabetes [9]. Higher weight, which is associated with insulin resistance, was inversely associated with urinary pH in a study of over 4800 patients with nephrolithiasis [34].

Although low urinary pH is a major risk factor for uric acid nephrolithiasis [10, 11], an impaired ability to excrete acid also could increase the risk for calcium-containing kidney stones by decreasing the urinary excretion of citrate [13]. In addition, the compensatory hyperinsulinemia of type 2 diabetes may increase the supersaturation of the urine with respect to calcium salts. Over 30 years ago, seminal work demonstrated that the ingestion of glucose or sucrose decreased the tubular reabsorption of filtered calcium [35] and increased urinary calcium excretion [36]. Subsequent animal experiments showed that this "carbohydrate-induced calciuria" could be inhibited by pharmacologically blocking the pancreatic secretion of insulin [37]. Experiments in humans undergoing euglycemic hyperinsulinemic clamp suggest that insulin, by an unknown mechanism, may increase the fractional excretion of calcium [14–16].

The prospective analysis in the male cohort failed to find an association between diabetes mellitus and the risk of incident stone formation, a result that differed from the cross-sectional analysis in men and both the cross-sectional and prospective analyses in older and younger women. This may be due to the older age (nearly 61 years) of diabetics in the male cohort at the start of the study. Because insulin resistance and compensatory hyperinsulinemia can precede the diagnosis of type 2 diabetes mellitus by decades [6], and because we excluded men with a history of kidney stones at baseline, our prospective analysis may have included diabetic men who were unlikely to develop kidney stones.

Because a kidney stone is unlikely to cause diabetes directly, the positive association between nephrolithiasis and subsequent diabetes suggests that a common metabolic defect may contribute to the development of both diseases. Insulin resistance and compensatory hyperinsulinemia could manifest as an increased susceptibility to kidney stones years before the actual diagnosis of diabetes. Stone formers were more likely to take thiazide diuretics, and these medications may increase the risk of type 2 diabetes [38]. However, we adjusted our analysis for the use of thiazide diuretics.

The limitations of our study deserve mention. We did not confirm all self-reported cases of incident type 2 diabetes, and some participants with diabetes at baseline may have had type 1 diabetes. However, these misclassifications are likely to be random with respect to case status, and therefore would bias the study results toward the null. The generalizability of our results also may be limited. Only a small proportion of our study population is non-white, and we do not have data on stone formation in men younger than 40 years of age. It is unknown whether age and race modulate the effect of insulin on urine composition. Finally, we currently lack 24-hour urine samples and stone composition analyses from most of the participants in our study. Thus, we were unable to determine if diabetes increases the risk of certain stone types, such as uric acid, but not others.

CONCLUSION

Diabetes mellitus is associated with an increased risk of kidney stone formation. Our study also demonstrates that a history of kidney stones increases the likelihood of a subsequent diagnosis of type 2 diabetes. Because this relation may be due to subclinical insulin resistance, it is reasonable to screen new stone formers for diabetes. Our study provides further evidence that nephrolithiasis is a systemic metabolic disorder, and suggests that the incidence and prevalence of stone disease will continue to increase as type 2 diabetes becomes more common.

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