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Cholelithiasis and Risk of Nephrolithiasis

Eric N. Taylor, MD, MSc^{1,3}, Andrew T. Chan, MD, MPH^{1,4}, Edward L. Giovannucci, MD, ScD^{1,5}, and Gary C. Curhan, MD, ScD^{1,2,5}

¹Channing Laboratory, Brigham and Women's Hospital, Boston, MA

²Renal Division, Department of Medicine, Brigham and Women's Hospital, Boston, MA

³Division of Nephrology and Transplantation, Maine Medical Center, Portland, ME

⁴Gastrointestinal Unit, Massachusetts General Hospital, Boston, MA

⁵Departments of Epidemiology and Nutrition, Harvard School of Public Health, Boston, MA

Abstract

Purpose—Existing data on the relation between gallstones (GS) and kidney stones (KS) are provocative but limited. Our goal was to determine whether symptomatic radiographically confirmed GS (and/or cholecystectomy) and symptomatic KS disease are independently associated.

Materials and Methods—We conducted cross-sectional and prospective analyses in the Nurses' Health Studies I and II (older and younger women, respectively) and the Health Professionals Follow-up Study (men) that included over 240,000 participants followed for 14 to 24 years. Regression models adjusted for age, body size, thiazide use, diet, and other factors.

Results—At baseline, the multivariate odds ratio of KS history in individuals with GS history compared to individuals without was 1.65 (95 % CI 1.46–1.86) in older women, 1.85 (95% CI 1.65–2.07) in younger women, and 1.61 (95% CI 1.41–1.85) in men. Prospectively, the multivariate relative risk of incident KS in participants with GS history compared to participants without was 1.26 (95 % CI 1.09–1.44) in older women, 1.32 (95% CI 1.14–1.52) in younger women, and 1.28 (95% CI 1.03–1.57) in men. The multivariate relative risk of incident GS in participants with KS history compared to participants without was 1.17 (95 % CI 1.06–1.29) in older women, 1.31 (95% CI 1.19–1.45) in younger women, and 1.51 (95% CI 1.35–1.68) in men. Prospective “lag” analyses instituting a delay of 4 years between the diagnoses of GS and KS yielded similar results.

Conclusions—GS and KS are independently associated. Additional studies are needed to identify shared mechanisms underlying both diseases.

Keywords

Kidney stones; gallstones; risk factors

Nephrolithiasis is a systemic disease. A wide variety of diseases (including obesity, hypertension, diabetes, and gout) are associated with kidney stones.^{1–5} In a recent study of the Atherosclerosis Risk in Communities (ARIC) cohort, individuals with a history of

Contact information for corresponding author: Eric N. Taylor, MD, MSc, Division of Nephrology and Transplantation, Maine Medical Center, 22 Bramhall Street, Portland, ME 04102, entaylor@partners.org, Phone: (207) 662-5672, Fax: (207) 662-6306.

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gallstones were 54% more likely to report a history of nephrolithiasis after adjusting for age, gender, body size, and other factors.⁶

Although novel and potentially important, the ARIC data linking gallstones and kidney stones are limited. First, ARIC did not account for diet. Lower intakes of many factors, such as fruit, vegetables, magnesium, coffee, and alcohol, are shared risk factors for gallstones and kidney stones.^{7–12} Second, the majority of the ARIC data were cross-sectional. There was inadequate statistical power in ARIC to examine prospectively the association between gallstone history and risk of incident kidney stones. Third, detection bias may account for the ARIC findings. Abdominal imaging used to diagnose gallstones may identify incidental kidney stones, and vice versa.

To determine whether gallstone disease is independently associated with nephrolithiasis, we performed cross-sectional and prospective studies in three large cohorts including over 240,000 participants: the Nurses' Health Studies (NHS) I and II and the Health Professionals Follow-up Study (HPFS). To minimize detection bias, we limited our study to symptomatic gallstones and kidney stones, employed lag-time analyses, and performed sub-analyses restricting gallstone "cases" to cholecystectomy.

MATERIALS AND METHODS

Study population

In 1976, 121,700 female nurses between the ages of 30 and 55 years enrolled in NHS I by completing an initial questionnaire that provided detailed information on medical history, life style, and medications. This cohort, like NHS II and HPFS, is followed by biennial mailed questionnaires, which include inquiries about newly diagnosed diseases. In 1989, 116,430 female registered nurses between the age of 25 and 42 years enrolled in NHS II by completing an initial questionnaire. 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 an initial questionnaire.

Ascertainment of gallstone disease

In NHS I, biennial questionnaires were used to assess occurrence and date of cholecystectomy. Of 50 randomly selected nurses who self-reported cholecystectomy, all 43 who agreed to requests for additional information reiterated their earlier report. Cholecystectomy was confirmed in all 36 nurses for whom medical records were available.

For NHS II and HPFS, the primary outcome was incident symptomatic gallstones and/or cholecystectomy. On biennial questionnaires, participants were asked whether they had undergone a cholecystectomy or had been diagnosed as having gallstones by a physician. Participants were also asked whether the diagnosis had been confirmed radiographically and whether their gallstones were symptomatic. To verify self-reported gallbladder disease, including cholecystectomy and diagnosed but unremoved gallstones, a random sample of 441 medical records of HPFS participants were reviewed. The diagnosis was confirmed in 99%.

Ascertainment of kidney stones

In prospective analyses, the primary outcome was an incident kidney stone accompanied by pain or hematuria. Participants reporting a new kidney stone on the biennial questionnaire were sent an additional questionnaire to determine the date of occurrence and symptoms.

We obtained medical records from 194 NHS I, 858 NHS II, and 582 HPFS participants who reported a kidney stone. In each cohort, 95% of the records confirmed the diagnosis. Of kidney stone records that included composition data, the majority (77%) contained 50% calcium oxalate.

Ascertainment of covariates

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 nutritional supplements. The food-frequency questionnaire (FFQ) has been mailed to study participants every 4 years. The reproducibility and validity of the FFQs have been documented.^{13, 14}

Nutrient intake was computed from the reported frequency of consumption of each specified unit of food and from USDA data on nutrient content. Nutrient values were adjusted for total caloric intake.^{15, 16} The intake of supplemental calcium in multivitamin or isolated form was determined by the brand, type, and frequency of reported use.

Information on age, weight, weight in early adulthood (age 21 in men and age 18 in women), and height was obtained on the baseline questionnaire. Self-reported weight was updated every two 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.¹⁷ Self-reported measures of waist and hip size also have been validated.¹⁷

Information on hypertension and diabetes mellitus was obtained from biennial questionnaires. The validity of these self-reported diseases has been documented.^{18–20} Information on thiazide diuretic use also was obtained from biennial questionnaires.

Statistical analysis

Cross-sectional analyses assessed kidney stone prevalence according to presence or absence of gallstone disease at baseline. Categorical variables were compared using the chi-square test and continuous variables compared using ANOVA. Logistic regression was used to control for the following baseline covariates: age (continuous), body mass index (six categories), use of thiazide diuretics (yes or no), family history of kidney stones (yes or no), history of hypertension (yes or no), history of diabetes (yes or no), alcohol intake (seven categories), supplemental calcium use (four categories), and the intakes of fluid, dietary calcium, animal protein, potassium, sodium, magnesium, sucrose, and caffeine (quintiles).

For each cohort, we performed two prospective analyses. The first analysis evaluated gallstone disease (updated every two years) as a risk factor for incident symptomatic kidney stones. Participants reporting a history of kidney stone disease at baseline were excluded. The second evaluated a history of kidney stones (updated every two years) as a risk factor for the development of incident gallstone disease. Participants reporting gallstone disease at baseline were excluded.

Person-months of follow-up were counted from the date of return of baseline questionnaire (1980 for NHS I, 1991 for NHS II, and 1986 for HPFS) to the date of incident case or death or to end of follow-up (May 31, 2004 for NHS I, May 31, 2005 for NHS II, and January 31, 2004 for HPFS). We allocated person-months according to exposure status at the start of each two-year follow-up period. To minimize the likelihood that radiographic imaging employed during a diagnosis of gallstone disease led to the diagnosis of a kidney stone, or vice versa, we also performed prospective “lag-time” sub-analyses that excluded incident cases of one disease diagnosed within 4 years of the other.

Cox proportional hazards was used to adjust for potential confounders. The covariates included in Cox models were the same as for logistic regression but were updated throughout the study.

Data were analyzed by using SAS software, version 9.1 (SAS Institute Inc., Cary, North Carolina). The research protocol for this study was approved by the institutional review board of Brigham and Women's Hospital.

RESULTS

Cross-sectional

Baseline characteristics of participants by history of gallstone disease are shown in Table 1. Participants with gallstone disease were older, had higher BMI, were more likely to use thiazide diuretics, and were more likely to report histories of hypertension, diabetes, and kidney stones.

A history of gallstone disease was independently associated with a history of nephrolithiasis in all three cohorts (Table 2). The multivariate odds ratio of history of kidney stone disease in participants with history of gallstone disease compared to participants without was 1.65 (95 % CI 1.46–1.86) in older women, 1.85 (95% CI 1.65–2.07) in younger women, and 1.61 (95% CI 1.41–1.85) in men.

Prospective

Incident kidney stone formation according to gallstone history—After excluding participants who reported a history of kidney stones at baseline, we prospectively studied 95,537 older women (NHS I), 101,587 younger women (NHS II), and 45,794 men (HPFS).

A history of gallstone disease was independently associated with an increased risk of incident kidney stones in all 3 cohorts (Table 3). The multivariate relative risk of kidney stone formation in participants with gallstone disease compared to participants without was 1.26 (95 % CI 1.09–1.44) in older women, 1.32 (95% CI 1.14–1.52) in younger women, and 1.28 (95% CI 1.03–1.57) in men. We also performed analyses restricting gallstone disease in NHS II and HPFS to cholecystectomy. The multivariate relative risk of kidney stone formation in participants with self-reported cholecystectomy compared to participants without was 1.59 (95% CI 1.05–2.41) in younger women and 1.66 (95% CI 1.18–2.35) in men.

Incident gallstone disease according to kidney stone history—After excluding participants who reported a history of gallstone disease at baseline, we prospectively studied 97,185 older women (NHS I), 99,605 younger women (NHS II), and 48,900 men (HPFS).

A history of kidney stones was independently associated with an increased risk of incident gallstone disease (Table 4). The multivariate relative risk of gallstone disease in participants with self-reported kidney stones compared to participants without was 1.17 (95 % CI 1.06–1.29) in older women, 1.31 (95% CI 1.19–1.45) in younger women, and 1.51 (95% CI 1.35–1.68) in men. We also performed analyses restricting incident gallstone cases in NHS II and HPFS to cholecystectomy. The multivariate relative risk of cholecystectomy in participants with self-reported kidney stones compared to participants without was 1.24 (95% CI 1.12–1.38) in younger women and 1.41 (95% CI 1.24–1.62) in men.

Adjustment for BMI decreased the magnitude of association between gallstone disease and kidney stones in women but not men. Adjustment for the following variables, instead of or in addition to categorical BMI, did not materially change the results: continuous BMI, BMI

squared, weight gain over the course of the study, weight gain since age 18 (in women) or age 21 (in men), BMI at age 18 (in women) or age 21 (in men), and waist circumference.

We also examined associations between gallstone disease and incident kidney stones (and vice versa) after instituting a delay of at least 4 years between the diagnoses of gallstones or kidney stones. The results of these prospective “lag-time” analyses were similar to results of the primary analyses.

Finally, the exclusion of participants with diabetes and hypertension did not materially change the results.

DISCUSSION

Our study found that gallstones were positively associated with nephrolithiasis, independent of age, body size, diet, and other factors. Gallstone disease was associated with prevalent kidney stones and also was associated with an increased risk of incident kidney stone formation. In addition, a history of kidney stones was associated with an increased risk of incident gallstone disease.

In a recent cross-sectional study of 12,161 ARIC participants, Akoudad and colleagues also reported that a history of gallstones was associated with prevalent nephrolithiasis.⁶ Although the odds ratios in ARIC were not adjusted for shared dietary risk factors for gallstone and kidney stone disease (such as lower intakes of fruit, vegetables, magnesium, coffee, and alcohol), the magnitudes of association in ARIC were similar to ours. In contrast to our prospective analyses, the ARIC investigators did not observe a statistically significant association between gallstone disease and subsequent risk of incident kidney stones. However, only 94 incident kidney stones were documented in ARIC, which limited statistical power.

Because abdominal imaging used to diagnose gallstones may identify incidental kidney stones, and vice versa, detection bias may account for the association between the two diseases. However, we used 3 strategies to minimize detection bias. First, unlike ARIC, we only considered symptomatic gallstones and symptomatic kidney stones. Second, we performed sub-analyses restricting the definition of a gallstone “case” to cholecystectomy. Symptomatic gallstones are the primary indication for cholecystectomy. Finally, we employed “lag-time” sub-analyses in our prospective studies that excluded incident cases of one disease diagnosed within 4 years of the other. Such analyses minimize the likelihood that radiographic imaging employed during a diagnosis of gallstone disease led to the diagnosis of a kidney stone, or vice versa.

The mechanisms underlying the association between gallstone disease and kidney stones are unknown. It is difficult to speculate on the nature of a shared metabolic defect that would predispose to the development of both diseases. Insulin resistance is associated with an increased risk of gallstones and kidney stones^{21, 22} but adjustment for larger BMI and greater waist circumference, which are strongly associated with insulin resistance, did not decrease the magnitude of association between gallstone and kidney stone disease in the men in our study.

Factors affecting the intestinal handling of bile acids and oxalate may account for the associations between gallstones and kidney stones in our study. Lower biliary concentrations of bile acids increase the risk for cholesterol gallstones, the most common type of gallstone, and can result from impaired enterohepatic circulation of bile salts.^{23, 24} Severe states of intestinal malabsorption can lead to reduced intestinal bile acid reabsorption and simultaneous increases in urinary oxalate (via reduced intestinal oxalate secretion or

increased absorption of dietary oxalate).²⁵ It is possible that subtle, and more common, conditions of intestinal malabsorption also may disrupt the normal enterohepatic circulation of bile acids while resulting in small but clinically relevant increases in urinary oxalate.

Other abnormalities in the intestinal tract may account for the link between gallstones and nephrolithiasis. For example, shifts in the intestinal microbial flora may play a role in the pathogenesis of both diseases. Colonization with *Oxalobacter formigenes*, an anaerobic Gram-negative bacterium that metabolizes intestinal oxalate, may decrease the risk of calcium oxalate kidney stones,^{21, 26} and a variety of bacteria, including *Helicobacter pylori*, may increase the risk of cholesterol gallstones.²⁷ However, we are unaware of data suggesting that intestinal colonization with *Oxalobacter* is associated with lower rates of *Helicobacter* infection.

Finally, it is possible that shared alterations of water and/or ion transport in the biliary epithelia and the kidney predispose to gallstones and kidney stones. The processing of bile in the gallbladder, which includes concentration, acidification, and calcium reabsorption, is complex and is mediated in part by a number of epithelial water and ion channels that also affect urine composition.^{23, 28} For example, aquaporins likely play an important role in water transport across human gallbladder epithelium.²⁸ Because higher bile calcium concentrations are a risk factor for pigment gallstones (and also may play a role in the pathogenesis of cholesterol gallstones),^{23, 29,30} it is intriguing to consider the possibility of an unknown “channelopathy” that increases calcium content in both bile and urine.

Our study has limitations. Because our study is observational, there may be confounding by unknown factors. The generalizability of our results also may be limited. Only a small proportion of our study population is non-white. Finally, we currently lack 24-hour urine samples from most of the participants with gallstones in our study. Thus, we are unable to compare the urinary excretion of lithogenic factors in individuals with and without gallstone disease.

CONCLUSIONS

Gallstones and kidney stones are independently associated. Our study provides further evidence that nephrolithiasis is a systemic disorder. Additional research identifying the shared mechanism(s) underlying the association between gallstones and kidney stones may lead to new treatment and prevention strategies for both diseases.

Acknowledgments

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Table 1

Age-adjusted baseline characteristics of older women (NHS I), younger women (NHS II), and men (HPFS) by gallstone history. *

	Gallstone history		P value
	Yes	No	
NHS I			
Number (%)	6,971 (8%)	80,587 (92%)	
Age, years **	48	46	<0.001
BMI, kg/m ² **	27	24	<0.001
Current thiazide use (%)	15%	9%	<0.001
Dietary intakes			
Potassium (mg/d)	2752	2757	0.54
Magnesium (mg/d)	291	294	<0.001
Caffeine (mg/d)	388	397	0.01
Alcohol (g/d)	4.9	6.5	<0.001
History of hypertension (%)	27%	15%	<0.001
History of diabetes (%)	5%	2%	<0.001
History of kidney stones (%)	5%	3%	<0.001
NHS II			
Number (%)	5694 (5%)	102,530 (95%)	
Age, years **	38	36	<0.001
BMI, kg/m ² **	29	25	<0.001
Current thiazide use (%)	5%	2%	<0.001
Dietary intakes			
Potassium (mg/d)	2913	2937	0.003
Magnesium (mg/d)	308	316	<0.001
Caffeine (mg/d)	259	244	<0.001
Alcohol (g/d)	2.1	3.2	<0.001
History of hypertension (%)	17%	6%	<0.001
History of diabetes (%)	3%	1%	<0.001
History of kidney stones (%)	7%	3%	<0.001
HPFS			
Number (%)	2004 (4%)	49,469 (96%)	
Age, years **	61	55	<0.001
BMI, kg/m ² **	27	26	<0.001
Current thiazide use	17%	10%	<0.001
Dietary intakes			
Potassium (mg/d)	3525	3444	<0.001
Magnesium (mg/d)	354	354	0.97
Caffeine (mg/d)	226	239	0.02

	Gallstone history		P value
	Yes	No	
Alcohol (g/d)	8.9	11.5	<0.001
History of hypertension	33%	22%	<0.001
History of diabetes	7%	3%	<0.001
History of kidney stones	14%	8%	<0.001

Note: NHS = Nurses' Health Study. HPFS = Health Professionals Follow-up Study. Dietary intakes of potassium, magnesium, and caffeine are energy-adjusted.

* 1980 for NHS I, 1991 for NHS II, and 1986 for HPFS

** Values expressed as means. BMI = Body mass index.

Table 2

Baseline odds ratios of prevalent nephrolithiasis according to gallstone history in older women (NHS I), younger women (NHS II), and men (HPFS). *

	Age-adjusted odds ratio	Multivariate odds ratio **
NHS I		
Gallstone history		
No	1.00 (reference)	1.00 (reference)
Yes	1.84 (1.63 to 2.07)	1.65 (1.46 to 1.86)
NHS II		
Gallstone history		
No	1.00 (reference)	1.00 (reference)
Yes	2.21 (1.99 to 2.47)	1.85 (1.65 to 2.07)
HPFS		
Gallstone history		
No	1.00 (reference)	1.00 (reference)
Yes	1.72 (1.51 to 1.96)	1.61 (1.41 to 1.85)

Note: NHS = Nurses' Health Study. HPFS = Health Professionals Follow-up Study.

* 1980 for NHS I, 1991 for NHS II, and 1986 for HPFS

** Odds ratios include 95% confidence intervals in parentheses. The multivariate model includes age, body mass index (6 categories), use of thiazide diuretics (yes or no), fluid intake (in quintiles), alcohol use (seven categories), family history of kidney stones (yes or no), history of hypertension (yes or no), history of diabetes (yes or no), calcium supplement use (four categories), and intake of calcium, animal protein, potassium, sodium, magnesium, sucrose, and caffeine (all in quintiles).

Table 3

Relative risk of incident symptomatic kidney stones according to gallstone history in older women (NHS I), younger women (NHS II), and men (HPFS). *

	Person-years	Incident kidney stones	Age-adjusted relative risk	Multivariate relative risk **
NHS I				
Gallstone history				
No	1,512,008	1195	1.00 (reference)	1.00 (reference)
Yes	226,580	268	1.50 (1.31 to 1.71)	1.26 (1.09 to 1.44)
NHS II				
Gallstone history				
No	1,061,940	1700	1.00 (reference)	1.00 (reference)
Yes	92,926	241	1.66 (1.45 to 1.90)	1.32 (1.14 to 1.52)
HPFS				
Gallstone history				
No	557,184	1585	1.00 (reference)	1.00 (reference)
Yes	31,170	97	1.37 (1.11 to 1.68)	1.28 (1.03 to 1.57)

Note: NHS = Nurses' Health Study. HPFS = Health Professionals Follow-up Study.

* Participants who reported kidney stones on the baseline questionnaire were excluded.

** Relative risks include 95% confidence intervals in parentheses. The multivariate model includes age, body mass index (6 categories), use of thiazide diuretics (yes or no), fluid intake (in quintiles), alcohol use (seven categories), family history of kidney stones (yes or no), history of hypertension (yes or no), history of diabetes (yes or no), calcium supplement use (four categories), and dietary intake of calcium, animal protein, potassium, sodium, magnesium, sucrose, and caffeine (all in quintiles).

Table 4

Relative risk of incident gallstones according to kidney stone history in older women (NHS I), younger women (NHS II), and men (HPFS).^{*}

	Person-years	Incident gallstones	Age-adjusted relative risk	Multivariate relative risk ^{**}
NHS I				
Kidney stone history				
No	1,494,591	8455	1.00 (reference)	1.00 (reference)
Yes	53,208	432	1.28 (1.16 to 1.41)	1.17 (1.06 to 1.29)
NHS II				
Kidney stone history				
No	1,056,970	6725	1.00 (reference)	1.00 (reference)
Yes	44,199	440	1.53 (1.39 to 1.69)	1.31 (1.19 to 1.45)
HPFS				
Kidney stone history				
No	562,174	2011	1.00 (reference)	1.00 (reference)
Yes	64,180	406	1.65 (1.48 to 1.84)	1.51 (1.35 to 1.68)

Note: NHS = Nurses' Health Study. HPFS = Health Professionals Follow-up Study.

^{*} Participants who reported gallstones on the baseline questionnaire were excluded.

^{**} Relative risks 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 (seven categories), history of hypertension (yes or no), history of diabetes (yes or no), calcium supplement use (four categories), and dietary intake of calcium, animal protein, potassium, sodium, magnesium, sucrose, and caffeine (all in quintiles).