

Kidney Stones Associate with Increased Risk for Myocardial Infarction

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ABSTRACT

Kidney stones are a risk factor for chronic kidney disease (CKD), which, in turn, is a risk factor for myocardial infarction (MI). The objective of this study was to determine whether kidney stones associate with an increased risk for MI. We matched 4564 stone formers (1984 through 2003) on age and gender with 10,860 control subjects among residents in Olmsted County, Minnesota. We identified incident MI by diagnostic codes and validated events by chart review through 2006. We used diagnostic codes to determine incidence of kidney stones and presence of comorbidities (CKD, hypertension, diabetes, obesity, dyslipidemia, gout, alcohol dependence, and tobacco use). During a mean of 9 years of follow-up, stone formers had a 38% (95% confidence interval 7 to 77%) increased risk for MI, which remained at 31% (95% confidence interval 2% to 69%) after adjustment for CKD and other comorbidities. In conclusion, kidney stone formers are at increased risk for MI, and this risk is independent of CKD and other risk factors.

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Kidney stones have been identified as a risk factor for chronic kidney disease (CKD).¹ Of great concern with the development of CKD is an increased risk for coronary heart disease. Reduction in both GFR and albuminuria is associated with coronary heart disease in the general population.^{2,3} It was hypothesized that the increased risk for CKD in individuals with kidney stones would lead to an increased risk for coronary heart disease. Alternatively, biological pathways that cause calcium kidney stones may also contribute to coronary artery calcification, a risk factor for coronary heart disease events. Myocardial infarction (MI) surveillance in Olmsted County, Minnesota, has been in place since 1979.^{4–7} We sought to determine whether kidney stone formers in Olmsted County were at an increased risk for

MI and whether this risk is related to the development of CKD.

A total of 5081 incident stone formers and 14,144 matched control subjects were identified from the Olmsted County general population between 1984 and 2003. The *International Classification of Diseases, Ninth Revision* (ICD-9) code used to identify stone formers was 592 (calculus of kidney and ureter) in 4467 (88%), 594 (calculus of lower urinary tract) in 613 (12%), and 274.11 (uric acid nephrolithiasis) in one (<1%). Prevalent MIs were similar between stone formers ($n = 178$ [3.5%]) and control subjects ($n = 489$ [3.5%]). After exclusion of individuals with prevalent MI and those who lacked clinic visits at least 90 days after the index date, 4564 stone formers and 10,860 control subjects were followed for incident MI. Only 2.1% of

these individuals were nonwhite, consistent with the racial distribution of the community (96% white in 1990). As a consequence of the matching, stone formers and control subjects were similar with respect to age (mean 44.6 *versus* 44.4 year), gender (59 *versus* 58% male), length of medical record documentation before the index date (mean 18.4 *versus* 21.9 years), and length of follow-up to last clinic visit or death (mean 8.7 *versus* 9.0 years). As shown in Table 1, stone formers were more likely than nonstone formers to have a baseline diagnosis of hypertension, diabetes, obesity, dyslipidemia, or gout and were less likely to have a diagnosis of alcohol dependence.

There were incident MIs in 96 stone formers and 166 control subjects. Stone formers were at increased risk for MI in analyses that were unadjusted (hazard ratio [HR] 1.43; 95% confidence interval [CI] 1.11 to 1.84; Figure 1), adjusted for age and gender (HR 1.38; 95% CI 1.07 to 1.77), further adjusted for CKD (HR 1.38; 95% CI 1.07 to 1.77), and fully ad-

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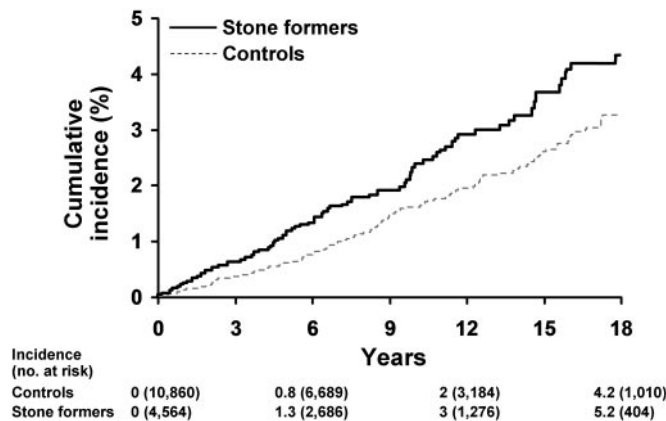
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Table 1. Baseline comorbidities in Olmsted County, Minnesota, stone formers and control subjects

Comorbidity	Stone Formers (n = 4564; n [%])	Control Subjects (n = 10,860; n [%])	P
CKD	116 (2.5)	200 (1.8)	0.0051
Hypertension	848 (18.6)	1748 (16.1)	0.0002
Diabetes	420 (9.2)	771 (7.1)	<0.0001
Obesity	1017 (22.3)	2155 (19.9)	0.0007
Dyslipidemia	860 (18.8)	1802 (16.6)	0.0007
Gout	135 (3.0)	255 (2.4)	0.028
Alcohol dependence	235 (5.2)	777 (7.2)	<0.0001
Tobacco use	619 (13.6)	1598 (14.7)	0.063

**Figure 1.** Increased risk for MI in stone formers than in controls among Olmsted County, Minnesota residents.

justed for all comorbidities (HR 1.31; 95% CI 1.02 to 1.69). The risk for MI remained with adjustment for the number of comorbidities (excluding alcohol dependence), age, and gender (HR 1.35; 95% CI 1.05 to 1.73). By coding subgroup, the risk for MI adjusted for age and gender was statistically significant for ICD-9 code 592 (HR 1.40; 95% CI 1.07 to 1.84) but not for ICD-9 code 594 (HR 1.24; 95% CI 0.70 to 2.21).

After adjustment for age and gender, most comorbidities were associated with MI: CKD (HR 2.97; 95% CI 1.86 to 4.72), hypertension (HR 1.54; 95% CI 1.18 to 2.01), diabetes (HR 2.18; 95% CI 1.61 to 2.94), obesity (HR 1.77; 95% CI 1.38 to 2.27), dyslipidemia (HR 1.65; 95% CI 1.27 to 2.15), gout (HR 1.40; 95% CI 0.88 to 2.22), alcohol dependence (HR 1.22; 95% CI 0.76 to 1.95), and tobacco use (HR 2.23; 95% CI 1.67 to 2.96). After exclusion of individuals with these comorbidities at baseline, there remained 2366 stone formers with 25 incident MIs and 5818 control subjects with 42 incident MIs, and the risk

for MI with kidney stones remained elevated but not statistically significant (HR 1.50; 95% CI 0.92 to 2.47). There was no detectable interaction between these comorbidities and the risk for MI with kidney stones ($P \geq 0.10$ for each comorbidity \times stone former interaction).

We found stone formers to be at a 38% increased risk for MI. A consideration is that this association reflects shared risk factors for both MI and kidney stones, namely, hypertension, diabetes, obesity, and dyslipidemia⁸; however, the risk for MI in stone formers remained elevated with adjustment for these and other known risk factors for MI, including CKD. This finding adds to the literature that kidney stones should be viewed as a metabolic disorder with clinical relevance beyond symptomatic urinary tract obstruction.⁹

A Medline (Ovid Technologies) search of English-language human studies on February 2010 with the terms “kidney/renal stone(s)/calculi or nephrolithiasis or urolithiasis” and “MI or coronary heart/ar-

tery disease” revealed 67 articles. Among these articles, there were six relevant studies, with most having small samples sizes.^{8,10–14} Several studies showed increased risk for MI in stone formers,^{8,10,12,14} and other studies showed no association.^{11,13} Lack of effective calcification inhibitors may be a common mechanism linking coronary artery calcification to calcium kidney stones (80% of stone formers).¹⁵ High-dosage calcium supplements may overwhelm calcification inhibitors and have been associated with an increased risk for both MI¹⁶ and kidney stones.¹⁷

The study strengths include general population cohorts with validated MI end points. Although there was likely some nondifferential misclassification of comorbidities by diagnostic codes, these comorbidities did have the expected associations with kidney stones and with MI. The risk for MI may vary by stone composition just as the risk for CKD may vary by stone composition.¹⁸ Limitations include lack of information on stone burden, stone composition, diet, medications, and laboratory test results. Furthermore, because study participants were mostly non-Hispanic white individuals, a population at increased risk for kidney stones,¹⁹ inferences to other ethnic groups are limited.

In conclusion, the increased risk for MI with kidney stones suggests these two diseases share a common pathophysiologic pathway. This could be a target for future intervention strategies. A history of kidney stones may also be a useful addition in risk stratification algorithms for MI. Further studies are needed to assess the relevance of stone composition and stone burden to risk for MI.

CONCISE METHODS

Study Population

Population-based research is feasible in Olmsted County because medical care is self-contained within the community. More than 95% of the population has at least one clinic visit with a health care provider in Olmsted County every 2 to 3 years, allowing complete enumeration of the local population. Diag-

nostic codes (manually or automatically coded from the final diagnoses in clinical notes) dating back to 1935 are indexed and linked among virtually all Olmsted County providers through the Rochester Epidemiology Project.²⁰ All Olmsted County residents with their first documented kidney stone in 1984 through 2003 were identified using ICD-9 codes 592, 594, and 274.11, as previously reported.¹ On manual review of 113 random charts, stone disease could be confirmed in 104 (92%).¹ Stone formers were matched 1:3 to control subjects among all Olmsted County residents on index date (first stone episode for stone formers and nearest clinic visit for non-stone formers) ± 5 years, duration of medical record before index date ± 5 years, age ± 5 years, and gender. Non-stone formers who developed a kidney stone after their index date were censored at that point and subsequently included in the incident stone former cohort with their own matched control subjects.

Outcome

The coronary heart disease surveillance system in Olmsted County used ICD-9 codes 410 to 414 to identify potential incident acute MI events from 1979 through 2006. Abstracters reviewed the medical record to document characteristic symptoms. A standardized classification algorithm using symptoms, cardiac biomarkers, and Minnesota coding of the electrocardiograms was applied to assign the diagnosis of MI.^{5,6} For identification of prevalent acute MIs before this period (1935 through 1978), ICD-9 code 410 and equivalent internal diagnostic codes (Berkson codes) were used.

Comorbidities

The initial dates of risk factors for MI were identified from ICD-9 codes. Risk factors identified were CKD, hypertension, diabetes, obesity, dyslipidemia, gout, alcohol dependence, and tobacco use.¹

Statistical Analysis

Individuals in the stone former and control cohorts were excluded from subsequent analyses for incident MI when they had a prevalent MI (before the index date). In addition, individuals with no follow-up clinic visits >90 days after the index date were

excluded. Individuals without incident MI were censored as of their last clinic visit, death (Minnesota death certificates), or on December 31, 2006, whichever came first. Because of these exclusions, matching was not retained in analyses. The association of kidney stones with subsequent MI was assessed using Kaplan-Meier plots and Cox proportional hazards models with adjustments for age, gender, CKD, and other comorbidities. Comorbidities were considered as both fixed (present before the index date) and time-dependent (developed after the index date) covariates. For assessment of validity of comorbidities by diagnostic codes, the risk for MI with each comorbidity was assessed in Cox models that adjusted for age and gender. Additional models assessed for interactions between each comorbidity and kidney stones on the risk for MI. Analyses used SAS 9.1 software (SAS Institute, Cary, NC).

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DISCLOSURES

None.

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