Original Article

The Risk of Coronary Heart Disease in Patients with Kidney Stones: A Systematic Review and Meta-analysis

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Abstract

Background: The reported risk of coronary heart disease (CHD) in patients with a history of kidney stones is conflicting. **Aims:** The objective of this meta-analysis was to assess the association between a history of kidney stones and CHD risk. **Materials and Methods:** A literature search was performed using MEDLINE, EMBASE, and Cochrane Database of Systematic Reviews from inception until April 04, 2014. Studies that reported odds ratios or hazard ratios comparing the risk of CHD in patients with a history of kidney stones versus those without a history of kidney stones were included. Pooled risk ratios (RRs) and 95% confidence interval (CI) were calculated using a random-effect, generic inverse variance method. **Results:** Seven study populations from four cohort studies and one cross-sectional study were identified and included in the data analysis. The pooled risk ratio (RR) of CHD in patients with kidney stones was 1.24 (95% CI, 1.10-1.40). This result remained significant (RR, 1.23 [95% CI, 1.08-1.41]) when the sensitivity analysis was restricted to only cohort studies. A history of kidney stones was associated with increased CHD risk in females (RR, 1.43 [95% CI, 1.12-1.82]), whereas the association was not significant in males (RR, 1.14 [95% CI, 0.94-1.38]). **Conclusions:** Our study demonstrates a statistically significant increased risk of CHD in female patients with prior kidney stones. This finding suggests that a history of kidney stones is a risk factor for CHD in females and may impact clinical management.

Keywords: Cardiovascular, gender, nephrolithiasis

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Introduction

Kidney stones have recently been linked to many comorbid conditions including hypertension, metabolic syndrome, diabetes, gout, and chronic kidney disease.[1] In addition, active and prior kidney stone formers are more likely to have accumulated risk factors for coronary heart disease (CHD).[2,3]

The reported risk of CHD in patients with a history of kidney stones, however, is still conflicting. Several studies have demonstrated an association between a history of kidney stones and CHD.[4-8] Conversely, a few studies have shown that a history of kidney stones is not a risk factor for CHD.[9-11] Tang *et.al.* found no association of prevalent kidney stone disease with all-cause and cardiovascular mortality.[12]

There is also controversy regarding CHD risk in male and female stone former groups. Elmfeldt *et.al.*[13] had previously reported an increased occurrence of kidney stones among male patients with myocardial infarction. More recent studies however show that CHD risk associated with a kidney stone is more pronounced for women than men.[2,14] The objectives of this meta-analysis were (1) to evaluate the association between a history of kidney stones and CHD risk and (2) to assess this association in different gender groups.

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Materials and Methods

Search strategy

Two investigators (W.C. and C.T.) independently searched published studies indexed in MEDLINE, EMBASE, and the Cochrane database from inception to April 2014 using the terms "kidney calculi", "nephrolithiasis", and "kidney stone" combined with the terms "coronary heart disease" and "cardiovascular disease". A manual search for additional relevant studies using references from retrieved articles was also performed. Conference abstracts and unpublished studies were excluded.

Inclusion criteria

The inclusion criteria were as follows:

1. Observational studies (case-control, cross-sectional or cohort studies) published as original studies to evaluate the association between kidney stones and CHD,
2. Odds ratios, relative risks, hazard ratios or standardized incidence ratio with 95% confidence intervals (CIs) were provided, and
3. A reference group composed of participants without a history of kidney stones was used.

Study eligibility was independently determined by the two investigators noted above. Differing decisions were resolved by mutual consensus. The quality of each study was independently evaluated by each investigator using Newcastle-Ottawa quality assessment scale.[10]

Data extraction

A standardized data collection form was used to extract the following information: Last name of the first author, title of the article, study design, year of study, country of origin, year of publication, sample size, characteristics of included participants, definition of CHD,[15] method used to diagnose kidney stones and CHD, mean duration of follow-up, and adjusted effect estimates with 95% CI. The two investigators mentioned above independently performed this data extraction.

Statistical analysis

Review Manager 5.2 software from the Cochrane Collaboration was used for data analysis. Point estimates and standard errors were extracted from individual studies and were combined by the generic inverse variance method of DerSimonian and Laird.[9] Given the high likelihood of between study variances, we used a random-effect model rather than a fixed-effect model.[16,17] Statistical heterogeneity was assessed using the Cochran's Q test. This statistic is complemented with the I^2 statistic, which quantifies the proportion of the total variation across studies that is due to heterogeneity rather than chance.[18] A value of I^2 of 0-25% represents insignificant heterogeneity, 26-50% low heterogeneity, 51-75% moderate heterogeneity, and >75% high heterogeneity.[19]

Results

Our search strategy yielded 130 potentially relevant articles; 117 articles were excluded based on title and abstract for clearly not fulfilling inclusion criteria on a basis of the type of article, study design, population, or outcome of interest. Thirteen articles underwent full-length article review. Four articles were excluded because they reported the incidence of CHD risk factors, not incidence of CHD. Three articles were excluded because they were descriptive study without control groups. An article was excluded because it reported mortality rate from CHD, not incidence of CHD. Seven study populations from five articles (four cohort studies and one cross-sectional study) with 52,791 patients with kidney stones met our inclusion criteria and were included in the data analysis.[2,4,7,11,14] Table 1 describes the detailed characteristics and quality assessment of the included studies.

The pooled risk ratio (RR) of CHD of subjects with kidney stones versus control subjects was 1.24 (95% CI, 1.10-1.40). The statistical heterogeneity was high with an I^2 of 84%. Figure 1 demonstrates the forest plot of the included studies. In addition, a history of kidney stones was associated with increased CHD risk in females (RR, 1.43 [95% CI, 1.12-1.82], I^2, 88%), whereas the association was not significant in males (RR, 1.14 [95% CI, 0.94-1.38], I^2, 87%). Figure 2 and Figure 3 show the forest plot of the included studies in females and males with kidney stones, respectively.

Sensitivity analysis

We performed a sensitivity analysis excluding the study by Domingos *et al.*[4] as this study was the only study with cross-sectional design, which could not establish a temporal relationship between kidney stones and CHD. The result remained significant (RR, 1.23 [95% CI, 1.08-1.41], I^2, 86%).

Evaluation for publication bias

Funnel plot to evaluate publication bias is fairly asymmetric and, thus, providing a suggestion to the presence of publication in favor of positive studies.

Discussions

Our meta-analysis demonstrated a significant association between a history of kidney stones and coronary

Table 1: Main characteristics of the studies included in this meta-analysis

	Alexander *et al.*[2]	Ferraro *et al.*[14]	Rule *et al.*[7]	Domingos *et al.*[4]	Westlund *et al.*[11]
Country	Canada.	United States.	United States.	Portugal.	Norway.
Study design	Retrospective cohort	Prospective cohort	Retrospective cohort	Cross-sectional	Retrospective cohort
Year	2014	2013	2010	2010	1973
Cases	All patients who were diagnosed with renal stone between 1997 and 2009. Cases were identified by using Alberta Kidney Disease Network database, which incorporates data from Alberta Health (the provincial health ministry).	Incident and prevalent cases of renal stone from three cohorts that followed participants from 1986 to 2010 (The Health Professionals Follow-up Study, The Nurses' Health Study I, and The Nurses' Health Study II).	All patients in Olmstead county who were diagnosed with renal stone between 1984 and 2003. Cases were identified by using database of Rochester Epidemiology Project.	Patients identified via Portuguese National Health Survey, which uses direct standardized interviews. Samples were randomly selected from the whole country of Portugal.	All male patients admitted to Ulleval hospital between 1892 and 1932 with a diagnosis of renal stone. Cases were identified by medical record review.
Diagnosis of stone	Diagnostic code from the registry.	Self-report.	Diagnostic code from the registry.	Based on patients' report during the interview.	Medical record review.
Controls	The rest of participants in the cohort.	Male veterans without sarcoidosis who were admitted at the same time period.	Sex and age subjects randomly selected from same database.	The remaining participants in the survey.	Observed incidence per expected incidence ratio was used. Expected incidence is calculated from the national MI incidence rates, taking account of the sex and age.
Definition of CAD	Hospitalization for AMI.	MI, fatal coronary heart disease or coronary revascularization procedure.	AMI.	MI.	MI.
Diagnosis of CAD	Diagnostic code from the same registry.	Self-report + medical record review.	Diagnostic code from the same database + medical record review.	Based on patients' report during the interview.	Diagnostic code from Oslo population registers.
Follow up	Until diagnosis of AMI, death, emigration from the system or March 31, 2009.	Until diagnosis of CHD, death or end of follow-up.	Until diagnosis of MI, death, or December 2006.	NA.	Until death 1961.
Average age of cases, Y	46.0	NA.	44.6	NA.	NA.
Male, %	64.1	18.9	59.0	NA.	100.0
Number of cases	25,532	19,678	4564	1701	1316
Number of control	3,169,920	222,427	10,860	21,648	NA.
Average duration of follow-up, Y	11.0	16.5	8.7	NA.	5.5
Confounder adjusted	Age, sex, aboriginal status, social assistance, residence location, and comorbid conditions.	Age, race, residence location, comorbid conditions, family history of CHD, medication used, menopausal status, smoking, BMI, alcohol, physical activity, and diet.	Age, gender, CKD, and comorbid conditions.	Age and BMI.	None.
Quality assessment (Newcastle-Ottawa scale)	Selection: 3 stars Comparability: 2 stars Outcome: 3 stars	Selection: 2 stars Comparability: 2 stars Outcome: 3 stars	Selection: 4 stars Comparability: 2 stars Outcome: 3 stars	NA.	Selection: 3 stars Comparability: 1 star Outcome: 1 star

AMI = acute myocardial infarction, BMI = body mass index, CHD = coronary heart disease, CKD = chronic kidney disease, MI = myocardial infarction, NA = not applicable.

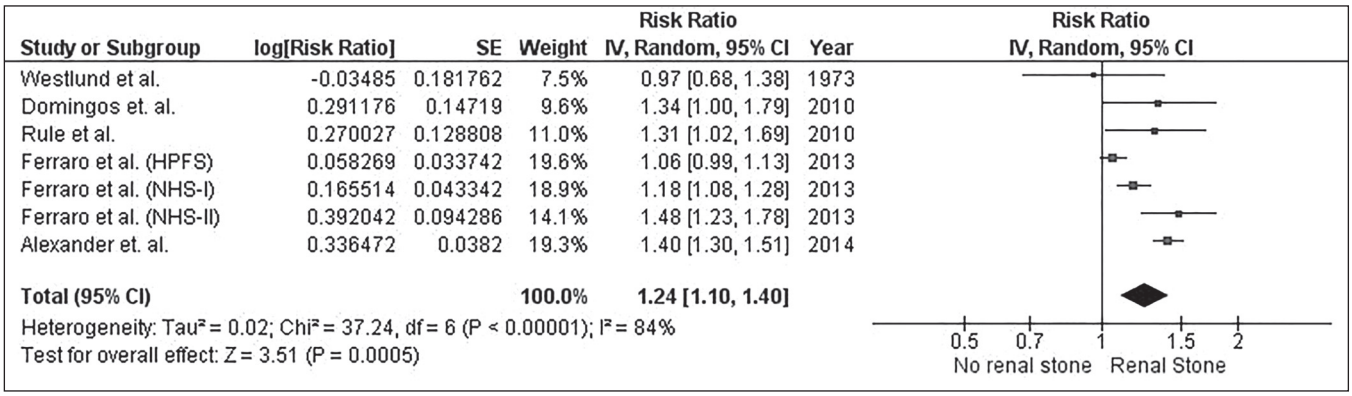

Figure 1: Forest plot of the included studies comparing risk of CHD between patients with a history of kidney stones and those without a history of kidney stones

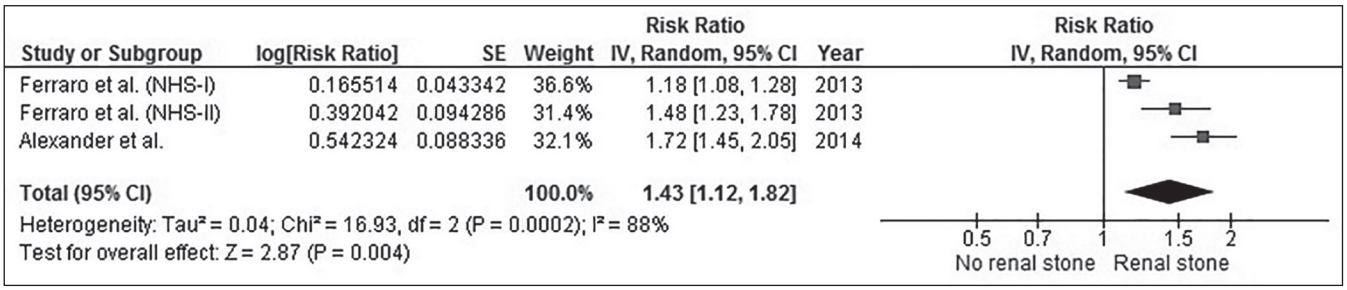

Figure 2: Forest plot of the included studies comparing risk of CHD in females with a history of kidney stones and those without a history of kidney stones

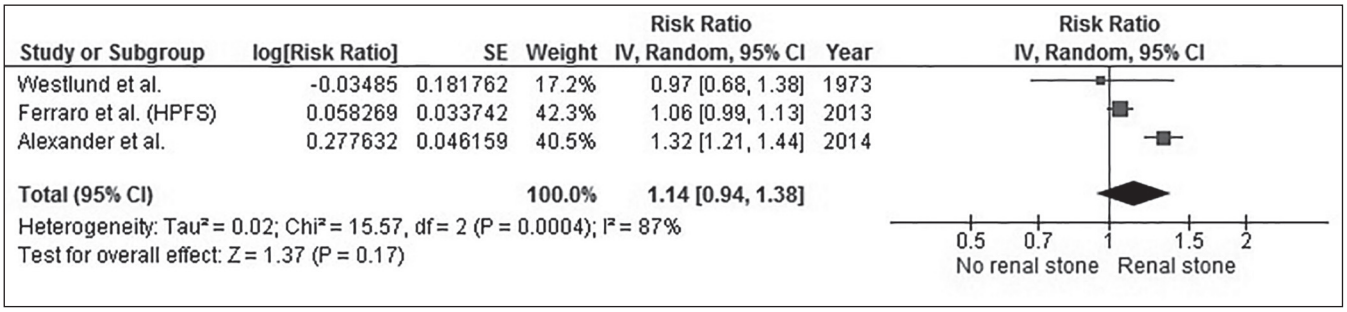

Figure 3: Forest plot of the included studies comparing risk of CHD in males with a history of kidney stones and those without a history of kidney stones

artery disease, with an overall 1.24-fold increased risk compared with those without a history of kidney stones. This association remained significant following sensitivity analysis restricted to cohort studies.

There are several plausible explanations for the increased risk of CHD in patients with kidney stones. First, kidney stones may be the manifestation of a systemic disorder.[20] A tendency to form stones has been associated with features of the metabolic syndrome, including obesity, hypertension and dyslipidemia.[5,8,21] Second, stone formers, especially those with uric acid stones, have demonstrated a significantly higher prevalence of diabetes and glucose intolerance.[21,22] Schwille *et al.*[23] found an association between postprandial insulinemia and increased urinary calcium and phosphorus excretion in patients with kidney stones.

A history of kidney stones has been demonstrated to be independently associated with CHD even after multivariable analysis for CHD risk factors.[2,4,7,14] These findings raise the hypothesis that urinary stone formation in the renal tubule has a vascular pathogenesis.[8] The underlying pathophysiology leading to calcium precipitation in the coronary arteries might also result from the same mechanism contributing to calcium precipitation in the renal tubules.[2] Khan *et al.*[24] recently found that the composition of vascular plaques are identical to Randall's plaque, the nidus of stone formation.[24] In addition, pyrophosphates, inhibitors of

calcification are found both in blood and urine.[25] The deficiency of pyrophosphates both in blood and urine could explain the association between CHD and kidney stone formation.

The prevalence of kidney stones, however, is higher in males than females (10.6% vs 7.1%, respectively).[26] Coronary heart disease is also more common in males than in females (7.8% vs 4.6%).[1,27] Therefore, it is surprising that our study found that females with kidney stone were significantly more likely to develop CHD. The underlying pathophysiology remains unclear. Females with kidney stones may also be exposed to unknown factors that could increase their risk of CHD. Further studies are needed to identify the potential risk factors of CHD in females with kidney stones such as dietary, estrogen/progesterone, pregnancy, muscle to fat composition, and genetic factors. A history of kidney stones in women may be added as a possible cardiac risk factor.

Even though most of the included studies were of high quality[2,7,14] (as evaluated by Newcastle-Ottawa scale), there are some limitations. First, two studies[2,7] were conducted using medical registry-based databases; therefore, coding inaccuracies for both kidney stones and CAD may have been presented. Another two studies[4,14] used a definition of kidney stones composed of self-reporting, which reported as accurate in 97% of cases.[28] Second, there is statistical heterogeneity in this complete analysis. The difference in the definition of CHD may be one of the main sources of this heterogeneity. Two studies included only patients with acute myocardial infarction[2,7] whereas the other studies had a broader definition that included patients with old myocardial infarctions[4,11,14] and patients undergoing coronary artery interventions.[14] Third, this is a meta-analysis of observational studies with its inherent limitations. Hence, at best, it can demonstrate an association but not a causal relationship. Observational studies require multivariable adjustments that may fail to account for unanticipated or unknown confounders. Future studies are required to identify the mechanisms underlying this potential causal relationship and to assess the types of the kidney stone and their association with CHD.

Conclusion

Our study demonstrates a statistically significant increased risk of CHD in female patients with prior kidney stones. This finding suggests that a history of kidney stones is a risk factor for CHD in females and may impact clinical management. Physicians should be aware of this potential increased risk.

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