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Original article

The association between urinary calculi and increased risk of future cardiovascular events: A nationwide population-based study

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ABSTRACT

Background: Although accumulating evidence suggests urinary calculi may be associated with an increased risk of cardiovascular disease (CVD), the number of longitudinal studies linking urolithiasis to CVD events is limited. We investigated the association between urinary calculi and the risk of development of myocardial infarction (MI) and/or stroke in a nationwide, population-based cohort database in Taiwan.

Methods: Our analyses were conducted using information from a random sample of 1 million people enrolled in the nationally representative Taiwan National Health Insurance Research Database. A total of 81,546 subjects aged 18 years or above, including 40,773 subjects diagnosed with urinary calculi during the study period and a propensity score-matched 40,773 subjects without urinary calculi were enrolled in our study.

Results: During a 10-year follow-up period, 501 MI events and 1295 stroke events were identified. By comparison, the urinary calculi group had a higher incidence rate of MI occurrence (11.79 vs 8.94 per 10,000 person-years) and stroke (31.41 vs 22.45 per 10,000 person-years). Cox proportional hazard regression model analysis showed that development of urinary calculi was independently associated with higher risk of developing future MI (HR, 1.31; 95% CI, 1.09–1.56, $p = 0.003$), stroke (HR, 1.39; 95% CI, 1.24–1.55, $p < 0.001$), and total cardiovascular events (HR, 1.38; 95% CI, 1.25–1.51, $p < 0.001$).

Conclusions: Urinary calculi were associated with an increased risk of future cardiovascular events in the Asian population, which was consistent with the recent epidemiologic evidence in Western countries.

Introduction

Cardiovascular disease (CVD) remains a leading cause of morbidity and mortality in most industrialized countries despite the availability of effective preventive methods. Application of predictive characters to identify populations at high risk of developing CVD is an important issue for primary and secondary prevention of CVD events in the community [1].

Urinary calculi are a common genitourinary disorder with a worldwide lifetime incidence of 10–15%. The incidence of urinary calculi has been increasing among both adults and children over the past century [2,3]. Urinary calculi in developed

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countries predominantly involve the upper urinary tract, presented mostly as kidney stones, while bladder stones are found more frequently among people in developing nations [4]. The overall prevalence of kidney stones has increased from 3.8% (1976–1980) to 8.8% (2007–2010) in the USA [5]. In Asia, Japanese data have also revealed that the age standardized annual incidence of upper urinary tract stones has increased from 81.3/100,000 in men and 29.5/100,000 in women (in 1965) to 165.1/100,000 in men and 65.1/100,000 in women (in 2005) [6], reflecting the increasing trend of urinary calculi worldwide. Therefore, considering the relatively high and increasing incidence rate of urinary calculi, it is important to understand what sequelae may occur in subjects with stones.

Similar to atherosclerosis, urinary calculi have a higher incidence in men, which is found to increase with age. Significant associations between kidney stones and conventional risk factors of CVD such as metabolic syndrome [7], systemic hypertension [8,9], diabetes mellitus [10], subclinical atherosclerosis [11], and chronic kidney disease [12,13] have been mentioned previously. Although not fully consistent, accumulating evidence suggests patients with urinary calculi may be associated with an increased risk of CVD [14,15]. Early studies failed to demonstrate the association between urinary calculi and subsequent CV risk [16,17], but more recent observational studies have confirmed the association and further extended the association to long-term events including myocardial infarction (MI) [14,18] and ischemic cerebral infarction (stroke) [18,19], suggesting urinary calculi are not only a disease of the genitourinary tract but also a possible risk factor or marker for the incidence of future CV events. However, there are only a limited number of studies examining the influence of urinary calculi on cardiovascular event incidence in a longitudinal manner. Therefore, we conducted this study to investigate the association between urinary calculi and future risk of cardiovascular events, including MI and/or stroke, by using a nationwide, population-based cohort database in Taiwan.

Methods

Data source

In the current study, we used the Longitudinal Health Insurance Database (LHID) from 1995 to 2010, obtained from the National Health Insurance Research Database (NHIRD). The National Health Insurance Program was launched in Taiwan in 1995, and now covers 99% of Taiwan's population of 23 million people. The LHID is composed from 1 million beneficiaries randomly sampled from the original NHI beneficiaries. The LHID consists of de-identified secondary data released for research purposes. The database includes the entire registry and claims data from this health insurance system, ranging from demographic data to detailed orders from ambulatory and inpatient care. The accuracy of diagnoses in the NHIRD has been validated previously [20,21], and the NHIRD database has been used to investigate disease association under a nationwide population-based study design. The diseases were coded according to the *International Classification of Disease, Ninth Revision, Clinical Modification* (ICD-9-CM) diagnosis codes, 2001 edition.

Study design

The study was designed as a population-based longitudinal cohort study to evaluate the association between future cardiovascular risks among patients with urinary calculi. Two cohorts, the urinary calculi cohort and the matched cohort without urinary calculi were included in our study. The urinary calculi cohort consisted of patients with a fresh diagnosis of urolithiasis and with at least two ambulatory visits or hospitalization coding ICD-9 CM 592.x or 594.x between 2000 and 2010. To clearly evaluate the association between renal stone and future CV events, patients with the following characteristics were excluded: age less than 18 years, antecedent urinary calculi, any history of cerebrovascular event or MI, with follow-up period less than 30 days. The matched cohort without urinary calculi was extracted from the remaining patients in the LHID and consisted of patients who never received a diagnosis of urinary calculi. We applied the same exclusion criteria to the matched cohort without urinary calculi as had been applied the urinary calculi cohort. Then, we performed 1:1 matching analysis; i.e. for each patient in the urinary calculi cohort, we identified one matching control patient. These were frequency-matched according to gender and propensity score for the likelihood of diagnosis of urinary calculi as calculated from baseline covariates, using multivariate logistic regression analysis.

Baseline characteristics

Baseline demographics included age, gender, medical care utilization as calculated by ambulatory visits during the past one year, income, and level of urbanization. The Charlson Comorbidity Index (CCI) score was used to determine the severity of comorbidities [22]. With each increase in the level of the CCI score, there was a stepwise increase in the cumulative mortality, ranging from score 0 with a 10-year survival rate of 99%, to score 5 with a 10-year survival rate of 34% [22].

Data about concomitant medications as classified according to the WHO Anatomical Therapeutic Chemical Classification System were extracted. Medications were categorized as follows: antiplatelet agents, warfarin, angiotensin-converting-enzyme inhibitors, angiotensin II receptor blockers, beta blockers, calcium-channel blockers, diuretics, nitrate, statin, dipyridamole, steroid, estrogen, progesterone, non-steroidal anti-inflammatory drugs, selective serotonin re-uptake inhibitors, proton-pump inhibitors, and anti-hyperglycemic drugs.

Outcomes

The study endpoint was the occurrence of MI, stroke, and the aggregate total of all cardiovascular events, including MI and stroke, during the follow-up period [23]. MI was defined as hospitalization with primary diagnosis coding ICD-9CM 410.x [24,25]. Stroke was defined as hospitalization with primary diagnosis coding ICD-9CM 433.x, 434.x, or 436.x [26,27]. The accuracy of diagnosis of the aforementioned cardiovascular events was validated by our previous study [28]. Both cohorts were followed until December 31, 2010, death, or the occurrence of an outcome.

Statistical analysis

Descriptive statistics were used to describe the baseline characteristics of our cohort. Baseline characteristics of the two groups were compared using Pearson χ^2 tests for categorical variables; the independent *t*-test and Mann–Whitney *U* test for parametric and nonparametric continuous variables, respectively. The propensity score for the likelihood of urinary calculi was calculated by multivariate logistic regression analysis, conditional on the baseline covariates. The incidence rate of CVD in the two groups was calculated by Poisson distribution. The relative risk of CVD between groups was calculated with the hazard ratio (HR) from Cox regression models. Cox regression models were also performed on age, sex, CCI score, site of stone, and procedure for stone to examine their influences on the CVD incidence after