available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Stone Disease

Diabetic Severity and Risk of Kidney Stone Disease

Aviva E. Weinberg [a,*], *Chirag J. Patel* [b], *Glenn M. Chertow* [c], *John T. Leppert* [a]

[a] *Department of Urology, Stanford University School of Medicine, Stanford, CA, USA;* [b] *Stanford Center for Prevention Research, Department of Medicine, Stanford University School of Medicine, Stanford, CA, USA;* [c] *Division of Nephrology, Department of Medicine, Stanford University School of Medicine, Stanford, CA, USA*

Article info

Article history:
Accepted March 8, 2013
Published online ahead of print on March 17, 2013

Keywords:
Diabetes mellitus
Glycemic control
Insulin resistance
Kidney stone disease

Abstract

Background: The prevalence of kidney stone disease is rising along with increasing rates of obesity, type 2 diabetes mellitus (T2DM), and metabolic syndrome.
Objective: To investigate the associations among the presence and severity of T2DM, glycemic control, and insulin resistance with kidney stone disease.
Design, setting, and participants: We performed a cross-sectional analysis of all adult participants in the 2007–2010 National Health and Nutrition Examination Survey (NHANES). A history of kidney stone disease was obtained by self-report. T2DM was defined by self-reported history, T2DM-related medication usage, and reported diabetic comorbidity. Insulin resistance was estimated using fasting plasma insulin (FPI) levels and the homeostasis model assessment of insulin resistance (HOMA-IR) definition. We classified glycemic control using glycosylated hemoglobin A_1c (HbA_1c) and fasting plasma-glucose levels (FPG).
Outcome measurements and statistical analysis: Odds ratios (OR) for having kidney stone disease were calculated for each individual measure of T2DM severity. Logistic regression models were fitted adjusting for age, sex, race/ethnicity, smoking history, and the Quételet index (body mass index), as well as laboratory values and components of metabolic syndrome.
Results and limitations: Correlates of kidney stone disease included a self-reported history of T2DM (OR: 2.44; 95% confidence interval [CI], 1.84–3.25) and history of insulin use (OR: 3.31; 95% CI, 2.02–5.45). Persons with FPG levels 100–126 mg/dl and >126 mg/dl had increased odds of having kidney stone disease (OR 1.28; 95% CI, 0.95–1.72; and OR 2.29; 95% CI, 1.68–3.12, respectively). Corresponding results for persons with HbA_1c 5.7–6.4% and ≥6.5% were OR 1.68 (95% CI, 1.17–2.42) and OR 2.82 (95% CI, 1.98–4.02), respectively. When adjusting for patient factors, a history of T2DM, the use of insulin, FPI, and HbA_1c remained significantly associated with kidney stone disease. The cross-sectional design limits causal inference.
Conclusions: Among persons with T2DM, more-severe disease is associated with a heightened risk of kidney stones.

* Corresponding author. Department of Urology, Stanford University School of Medicine, 300 Pasteur Drive, Stanford, CA 94305, USA. Tel. +1 650 723 4537; Fax: +1 650 498 5346.
E-mail addresses: avivaw@stanford.edu, avivaw@gmail.com (A.E. Weinberg).

1. Introduction

Kidney stone disease is a painful and costly disease. Hospitalizations, interventions, and work days lost due to kidney stones impose a major economic burden, with total annual medical expenditures in the United States exceeding $2.1 billion in 2000 [1]. The lifetime prevalence of kidney stones is increasing, with data from the most recent National Health and Nutrition Examination Survey (NHANES; 2007–2010) reporting an 8.8% population

0302-2838/$ – see back matter
http://dx.doi.org/10.1016/j.eururo.2013.03.026

prevalence—a substantial increase from the 5.2% prevalence reported in a prior NHANES cohort [2]. US population studies have similarly documented a rise in the prevalence of obesity, metabolic syndrome, and type 2 diabetes mellitus (T2DM) [3,4]. Recent epidemiologic studies have demonstrated a significant association between dietary and lifestyle factors and kidney stone disease. Analyses from the Health Professionals Follow-up Study and the Nurses' Health Study I and II identified associations among obesity, T2DM, and incident kidney stone disease [5,6]. Pathophysiologic explanations for the increased risk of kidney stones in diabetics have largely focused on insulin resistance (IR). IR is associated with derangements in renal ammonium production, increased urinary acidification, hypocitraturia, and hypercalciuria, all of which can contribute to the development of uric acid and calcium stones [7–10].

T2DM is a leading cause of end-organ disease and death in the United States. There is a direct relation between the degree of hyperglycemia and the risk of complications of T2DM over time. Among persons with T2DM, poorer glycemic control and more pronounced IR are associated with the risk of microvascular disease, peripheral vascular disease, amputations, myocardial infarction, stroke, heart failure, and all-cause mortality [11].

Despite compelling epidemiologic data supporting the association of diabetes and kidney stones, little is known about how diabetic severity might modify the risk of kidney stone disease. In this study, we investigated associations among the presence and severity of T2DM, glycemic control, and IR with kidney stone disease in a nationally representative sample. We hypothesized that more severe T2DM would be associated with higher odds of having kidney stone disease.

2. Methods

2.1. Study population

NHANES is a program of studies conducted by the National Center for Health Statistics, which is a part of the US Centers for Disease Control and Prevention. These surveys are used to assess the health and nutritional status of adults and children in the United States. The NHANES interview includes demographic, socioeconomic, dietary, and health-related questions. The examination component consists of medical and physiologic measurements, as well as laboratory tests. The NHANES 2007–2010 survey is the most recent collection, and includes kidney stone-related data.

Participant health examinations, including biophysical measurements and blood and urine collections, were conducted in the NHANES mobile examination center. Questionnaires were administered to NHANES participants both at home and in the mobile trailer. The current study included participants in NHANES 2007–2010 who were aged ≥20 yr, underwent a health examination, and responded to the question "Have you ever had a kidney stone?"

2.2. Independent variables: diabetes and severity definitions

We used several methods to define the presence of T2DM: a self-reported history of DM, use of glucose-lowering medications (insulin or oral hypoglycemics), and self-reported diabetic comorbidities in the form of retinopathy. IR was estimated using fasting plasma insulin (FPI) levels and the homeostasis model assessment of IR (HOMA-IR) definition (FPI [milligrams per deciliter] multiplied by fasting glucose [milligrams per deciliter], and divided by a correction factor of 405). HOMA-IR is a method widely used in epidemiologic studies to quantify IR and beta-cell function. For FPI and HOMA-IR, these measures were grouped into tertiles, due to the absence of clinically relevant cut-off values and their skewed distributions. We categorized glycemic control using glycosylated hemoglobin A_1c (HbA_1c) and fasting plasma-glucose (FPG) levels as follows: FPG <100 mg/dl, 100–126 mg/dl, or ≥126 mg/dl; and HbA_1c <5.7%, 5.7–6.4%, or ≥6.5%, according to cut-offs recommended by the American Diabetes Association.

2.3. Dependent variable: prevalent kidney stones

The primary outcome for our analysis was the participant response on the medical questionnaire to "Have you ever had kidney stones?"

2.4. Other clinical characteristics

Age, sex, race/ethnicity, highest level of education, and household income were assessed by questionnaire. Individuals were grouped by age: 20–39 yr, 40–59 yr, and ≥60 yr. We used the racial/ethnic group variable reported by NHANES, classified as *non-Hispanic white, non-Hispanic black, Mexican American, other Hispanic*, and *other/multiracial*, and joined responses from the categories of *Mexican-American* and *other Hispanic* into a single Hispanic category according to the analytic guidelines. We used household income as a measure of socioeconomic status, and recategorized the income strata (in US dollars) as $0–19 999, $20 000–34 999, $35 000–74 999, and ≥$75 000. The Quételet index (body mass index [BMI], kg/m^2) was categorized using the World Health Organization cutoffs as lean or normal weight (<24.9 kg/m^2), overweight (25.0–29.9 kg/m^2), and obese (≥30.0 kg/m^2). Three or more consecutive blood pressure measurements were taken during the physical examination, with mean values of systolic blood pressure (SBP) and diastolic blood pressure (DBP) used for our analysis. Of the many laboratory parameters measured in NHANES, we considered serum uric acid, serum calcium, high-density lipoprotein (HDL), and triglyceride (TG) concentrations as laboratory correlates of stone risk and/or metabolic syndrome/T2DM.

2.5. Statistical methods

All statistical analyses were performed using SAS v9.3 software (SAS Institute Inc, Cary, NC, USA) and incorporated the recommended NHANES sample weights, strata, and cluster design variables. Graphics were constructed using R v2.15 software. We used the subsample fasting sampling weights in the glucose and insulin laboratory-collection component to appropriately account for NHANES's complex survey structure and produce estimates that were representative of the total, noninstitutionalized, civilian US population. To produce estimates with greater statistical reliability, we combined two 2-yr cycles of continuous NHANES (2007–2008 and 2009–2010).

We calculated the odds of kidney stone disease being associated with each demographic factor and individually with each self-reported and calculated measure of diabetic severity. We then constructed two multivariable regression models to analyze each diabetic severity measure. In model A, we adjusted for age, sex, race/ethnicity, smoking history, and BMI. In model B, we additionally included metabolic stone risk factors (serum uric acid and calcium levels), and selected metabolic syndrome traits (HDL <40 mg/dl, TG >150 mg/dl, and SBP >140 mm Hg or DBP >90 mm Hg). All statistical tests were two-sided and a p value <0.05 was considered statistically significant.