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Decreased renal function among adults with a history of nephrolithiasis: A study of NHANES III

DANIEL L. GILLEN, ELAINE M. WORCESTER, and FREDRIC L. COE

Department of Health Studies and Department of Medicine, University of Chicago, Chicago, Illinois

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Background. Although intuitively appealing, the hypothesis that nephrolithiasis is associated with decreased renal function has not thoroughly been investigated. Because the prevalence of nephrolithiasis and chronic renal disease in westernized societies has risen over the past three decades, we sought to determine if persons with a history of kidney stones have lower renal function relative to nonstone formers.

Methods. We used data from the Third National Health and Nutrition Examination Survey (NHANES III) to compare estimated glomerular filtration rate (GFR) between persons over age 30 with and without a history of kidney stones. In total, 876 persons with a history of stones, and 14,129 persons without stones were available for analysis.

Results. We observed that the association between history of stones and estimated GFR depends on body mass index (BMI) ($P = 0.004$). After adjustment for potential confounding factors, mean estimated GFR in stone formers with a BMI ≥ 27 kg/m^2 was 3.4 mL/min/1.73 m^2 lower than that of similar nonstone formers (95% CI −5.8, −1.1) ($P = 0.005$). No difference was found among persons with a BMI <27 kg/m^2. The probability of an overweight stone former having an estimated GFR between 30 and 59 mL/min/1.73 m^2 relative to a GFR above 90 mL/min/1.73 m^2 was nearly twice that of a similar nonstone former [relative risk ratio (RRR) = 1.87, 95% CI 1.06, 3.30].

Conclusion. Among overweight persons, nephrolithiasis may not merely be a disease of stones, but may also reduce kidney function. Further work in alternate study samples is needed to validate this finding and determine the mechanisms responsible.

The impact of chronic renal insufficiency (CRI) on public health has been well documented. The prevalence of elevated serum creatinine (>1.5 mg/dL in men and >1.4 mg/dL in women) in the Framingham Heart Study was estimated at 8.0% for men and 8.9% for women [1], while more than 300,000 persons in the United States have end-stage renal disease (ESRD) [2]. Alarmingly, the incidence of CRI is rising throughout the world [3]. With respect to patient outcomes, CRI patients suffer from an increased risk of mortality and cardiovascular disease relative to the general population [4, 5]. Given the number of persons at risk for CRI and the prognosis associated with the disease, identification of risk factors for the development of renal disease has become a top priority to researchers in the nephrology community.

As the incidence of CRI has risen over the past three decades, the frequency of nephrolithiasis in westernized societies has also increased. Recently, the prevalence of nephrolithiasis among 20- to 74-year-old patients in the United States was estimated to be 5.2% during the years 1988 to 1994, compared to 3.8% from 1976 to 1980 [6]. While much is known about the pathogenesis and treatment of nephrolithiasis [7], the clinical consequences of stone disease remain relatively unidentified. In particular, little is known about the effect of stone disease on renal function. Our hypothesis is that repeated transient obstruction from stone passage, treatments such as extracorporeal shock wave lithotripsy (ESWL), and possibly mineral deposits in the renal medulla may damage nephrons and reduce renal function [8–10]. The current study uses national health survey data collected during the years 1988 to 1994 to compare renal function, as measured by estimated glomerular filtration rate (GFR), between persons with and without a history of nephrolithiasis. We hypothesized that stone formers would have lower estimated GFR when compared to similar nonstone formers.

METHODS

Study population

Data from the NHANES III was used for this analysis. A detailed description of the methods used in the survey is available elsewhere [11]. Briefly, NHANES III was one of several periodic surveys conducted by the National Center for Health Statistics. The survey, conducted during 1988 to 1994, was designed to provide national estimates of health and nutritional status in the civilian noninstitutionalized United States population aged 2 months

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and older. Data collected in NHANES III included sociodemographic factors, medical history, health-related behaviors, and medication use. Ultimately, 33,994 persons were interviewed. In the current study, we limit our analysis to adults aged 30 to 90 years with information on the lifetime occurrence of kidney stones ($N = 15{,}005$). The choice to restrict our analysis to individuals over 30 years of age was based primarily on two factors. First, the prevalence of stones among individuals less than 30 years of age is quite low, yet these individuals carry great sampling weight in the NHANES survey (due to oversampling of the elderly). Thus, any conclusions drawn would be quite heavily influenced by a relatively small number of stone formers in this age group. Second, we hypothesized that the effect of nephrolithiasis on renal function is a cumulative one that may take many years to manifest. Thus by focusing on individuals over 30 years of age, this would provide ample time for the effects of stone disease on renal function to begin to develop.

Exposure and outcome definitions

The primary exposure in our analysis was any history of kidney stones. All participants over age 30 who answered "yes" to the question "Have you ever had a kidney stone?" ($N = 876$) were considered to have a history of nephrolithiasis. Persons who responded "don't know" ($N = 13$) or did not respond ($N = 8$) were excluded. The outcome of interest was taken to be renal function as estimated by the Modification of Diet in Renal Disease (MDRD) equation [12]. Thus, GFR was estimated as

$$\mathrm{GFR_{MDRD}} = 170 \times \mathrm{S_{Cr}^{-0.999}} \times \mathrm{age_{yrs}^{-0.176}} \times \mathrm{BUN^{-0.170}} \times \mathrm{S_{alb}^{0.318}} \times 1.180^{\mathrm{black}} \times 0.762^{\mathrm{female}}$$

where S_{Cr} denotes serum creatinine, BUN denotes blood urea nitrogen, and S_{alb} denotes serum albumin. Coresh et al [13] have reported that the assay used for measuring serum creatinine in the NHANES study resulted in creatinine levels systematically higher than those used to obtain the MDRD prediction model. As a consequence, they suggest creatinine values from NHANES III be recalibrated to account for an average overestimate of 0.23 mg/dL. All analyses presented here have performed the recommended recalibration.

Statistical analysis

All reported point estimates and standard errors incorporate the NHANES III survey weights which account for unequal probability of selection into the NHANES sample and survey nonresponse. Variance estimates were computed via the method of linearization [14]. Patient characteristics, adjusted for stone history and age, were compared using linear regression for continuous covariates and logistic regression for categorical covariates. Multiple linear regression was used to compare mean estimated GFR between stone formers and nonstone formers. Covariates identified as potential confounders in the relationship between estimated GFR and stone history were adjusted for. These included age, gender, race (African American vs. other), boxy mass index (BMI), systolic blood pressure, hemoglobin A_{1c} (HbA_{1c}), diabetes, history of cardiovascular disease (myocardial infarction, stroke, congestive heart failure), smoking status (ever vs. never), health insurance status, and use of prescription diuretics. Other covariates considered as adjustment variables but not presented here include alcohol use, selected dietary factors, including calcium intake, household income, and marital status. Multiplicative interactions between stone history and age, gender, race, diabetes, and BMI were formally tested. The presented analyses include adjustment for BMI as a continuous linear covariate. However, to address the potential for residual confounding by BMI, secondary analyses adjusting for BMI as a categorical covariate (based upon quintiles of the distribution) were also performed. As these results did not qualitatively change our findings, we have chosen to present models adjusting for BMI as a continuous linear covariate. In addition, a separate linear regression model among persons with a history of stones was conducted to examine the association between prior stone treatment and estimated GFR.

It was a priori hypothesized that stone formers would not merely experience a downward shift in the distribution of GFR, but that the distribution of GFR among stone formers would be skewed to the right, resulting in a higher proportion of persons in the lower-tail of the distribution of GFR. To test this hypothesis, estimated GFR was categorized using cut points suggested by the National Kidney Foundation's Kidney Dialysis Outcomes and Quality Initiative (K/DOQI) guidelines for classification of CRI: less than 30 mL/min per 1.73 m^2, 30 to 59 mL/min per 1.73 m^2, 60 to 89 mL/min per 1.73 m^2, and 90 mL/min per 1.73 m^2 or above [15]. Multinomial logistic regression was used to compare the relative risk of having an estimated GFR in a lower category relative to the highest category between persons with and without nephrolithiasis. Model based estimates are reported as relative risk ratios comparing stone formers with nonstone formers. Adjustment covariates included in the multinomial logistic regression included age, gender, race, BMI, systolic blood pressure, HbA_{1c}, diabetes, history of cardiovascular disease, smoking status, health insurance status, and use of prescription diuretics.

All statistical analyses were performed using conventional commercial software (Stata Corp. 2003, Stata Statistical Software, Release 8.0, College Station, TX, USA).