

Nephrolithiasis is associated with an increased prevalence of cardiovascular disease

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Running title: Nephrolithiasis and cardiovascular disease

Abstract

Background: Nephrolithiasis has been associated with hypertension, obesity and diabetes *Mellitus*. The prevalence of adverse cardiovascular outcomes among kidney stone formers (KSF) is unknown.

Methods: We examined the IV Portuguese National Health Survey for documenting possible associations between nephrolithiasis, cardiovascular diseases, diabetes and obesity in the Portuguese adult population.

Results: We obtained 23,349 questionnaires from individuals with ≥ 15 year-old. The prevalence of kidney stone disease was 7.3%. The prevalence of hypertension was higher among KSF when compared with the general population (50.4% vs. 30.2%; $p < 0,001$). Age and obesity significantly increase the risk for nephrolithiasis. After adjusting for age and body mass index, KSF have higher prevalence of hypertension (odds-ratio: 1.841; 95% CI: 1.651 – 2.053), diabetes *Mellitus* (odds-ratio: 1.475; 95% CI: 1.283 – 1.696; $p < 0.001$), myocardial infarction (odds-ratio: 1.338; 95% CI: 1.003 – 1.786; $p < 0.05$), and stroke (odds-ratio: 1.330; 95% CI: 1.015 – 1.743; $p < 0.05$) as compared with non-stone formers.

Conclusions: Kidney stone disease is associated with a higher prevalence of chronic diseases and adverse cardiovascular outcomes when compared with the general population.

Keywords: kidney stone disease; hypertension; obesity; diabetes *Mellitus*; cardiovascular risk; epidemiology

Introduction

Nephrolithiasis is a relatively prevalent disease in Western civilizations ¹. Epidemiological studies documented an association of nephrolithiasis with obesity, diabetes *Mellitus* and arterial hypertension ²⁻⁵. These comorbidities are manifestations of the metabolic syndrome and their high prevalence in KSF points to an involvement of insulin resistance in the pathophysiology of nephrolithiasis ^{6;7}. Obesity and diabetes promote lithogenesis: uric acid stones are more common in diabetic patients ⁸ and obesity increases the urinary excretion of promoters of crystallization, urine acidity, and contributes to an increase of calcium oxalate lithogenesis ^{9;10}. An increased risk of kidney stone formation was documented in obese individuals in a large prospective study ¹¹ and in individuals with a high fructose consumption ¹², a natural sugar implicated in the development of the metabolic syndrome in humans ¹³.

There is some evidence of an increase of the risk factors for coronary heart disease in KSF ¹⁴, but there are no available data to demonstrate that this enhanced risk actually results in adverse clinical outcomes in KSF.

The Portuguese National Health Survey (NHS) is an instrument of analysis with 25 years of experience conducted by the National Health Institute Doutor Ricardo Jorge and the National Institute of Statistics (NIS) of Portugal ¹⁵. This instrument meets the international guidelines of the World Health Organization (WHO) and the EUROSTAT regarding health questionnaires ^{16;17} and is based on a large probabilistic population sample, randomly selected among residents in Portuguese territory. The fourth NHS allowed us to study possible associations between nephrolithiasis and diabetes *Mellitus*, hypertension, myocardial infarction, and stroke.

Methods

The NHS is a validated questionnaire to collect responses for operating 233 variables, according to WHO recommendations for the development of health surveys. The data collection was carried out by direct interview. Interviewers were recruited by the NIS, being preferred not to have training in health sciences to prevent the know effect of focused interviews, and had specific training to conduct the interviews in sensitive areas. A pilot test was done in April 2005, , and data collection took place in 2005-2006, with a total duration of 52 weeks.

The existence of each chronic disease was coded in a dummy variable, according to the following criteria: a positive answer of the respondents on whether they have or had ever had the disease mentioned, plus a positive response whether that knowledge was transmitted to them by a physician or nurse. The age of onset of the disease and/or diagnosis, and the use of drugs or any other form of treatment were also asked. Anthropometric data collected at the time of questionnaires included weight and height. Obesity was defined as body mass index (BMI) ≥ 30 Kg/m².

Sample selection

The sample used in the 4th NHS was randomly selected from a mother-sample used by the NIS for studies with families among residents in private households from a representative sample of households from the mainland and the autonomous regions of Azores and Madeira, using a system of stratification and systematic selection. The stratification of the mother-sample was made at the level of the seven regions defined by the Nomenclature of Territorial Units for Statistics (NUTS II) of the European Community. The number of individuals selected within each region was scaled to ensure an equitable distribution across regions, according to the results of the 2001 census and the last NHS held in 1998.

The areas of the interview were selected approximately equally by quarter and week, to minimize possible seasonal effects of the survey results.

We used the questionnaires of all respondents aged ≥ 15 years-old and whose answers were provided directly to the interviewers; proxy answers were excluded.

Statistical methods

A descriptive statistics for all variables was carried out. Categorical variables were expressed as proportions and compared with the Chi-square. Binary logistic regression was used to analyze the effect of multiple explanatory variables on dichotomous variables. The average of the ordinal variables was compared using the Mann-Whitney's test. The t-test for independent variables was used to compare the means between interval variables.

Statistical analyses were conducted using SPSS® version 13.0 for Windows (SPSS Inc., U.S.A.). A p value < 0.05 was considered significant.

Results

We identified 23,349 surveys who met the inclusion requirements . The prevalence of nephrolithiasis in this population was 7.3%. Compared with individuals without a history of kidney stones, KSF were older (median of the age group: 50 – 54 vs. 60 – 64 years-old; $p < 0.001$) (Figure 1) and have a slightly higher BMI (26.0 ± 4.5 vs. 27.2 ± 4.6 kg/m²; $p < 0.001$).

The prevalence of hypertension, obesity, diabetes, stroke, and myocardial infarction was significantly higher in KSF than in the general population (Table 1).

After correction for age, the odds-ratio (O.R.) for obesity was 29% higher in the population with nephrolithiasis compared with non-stone formers (O.R.: 1.298; 95% CI: 1.151 – 1.464; $p < 0.001$).The odds-ratio for hypertension adjusted for age and

BMI was higher in KSF as compared to non-stone formers (O.R.: 1.84; 95% CI: 1.151 – 1.464; $p < 0.001$), and the age of onset of hypertension occurred earlier in the first group (49.2 ± 14.4 vs. 50.4 ± 14.4 years-old; $p < 0.05$; respectively).

Also for diabetes, the O.R. adjusted for age and BMI, was higher in KSF as compared to non-stone formers (O.R.: 1.475; 95% CI: 1.283 – 1.696; $p < 0.001$). We found no significant association between treatment for kidney stones and the development of diabetes. Only 489 of 1,701 KSF reported any kind of treatment for nephrolithiasis, 67 of them were diabetic and 422 were not ($P = NS$).

After adjustment for age and BMI, the probability of myocardial infarction (O.R. 1.338; 95% CI: 1.003 – 1.786; $p < 0.05$) and stroke (O.R.: 1.330; 95% CI: 1.015 – 1.743; $p < 0.05$) was increased in KSF as compared to non-stone formers. After further adjustment for the concomitant presence of hypertension and diabetes, the association of nephrolithiasis with stroke did not reach significance, and the association of nephrolithiasis with myocardial remained significant only in women (O.R.: 1.566; 95% CI: 1.001 – 2.448; $p < 0.05$).

In individuals who reported kidney stone disease and any other of the chronic diseases under study, in most cases the age at onset of nephrolithiasis preceded the age of development of clinical manifestations of those diseases. The average age difference between the initial manifestations of KSD and the appearance of the other chronic diseases was: hypertension 2.0 ± 15.7 years, $p < 0.001$; diabetes *Mellitus* 6.5 ± 14.7 years, $p < 0.001$; stroke 7.8 ± 13.3 years, $p < 0.001$; myocardial infarction 8.8 ± 17.5 years, $p < 0.001$ (Figure 2).

Discussion

This study identified significant associations between nephrolithiasis and hypertension, diabetes, myocardial infarction and stroke. Previous studies have documented an increased prevalence and incidence of hypertension in stone formers^{18;19} and a higher incidence of nephrolithiasis in hypertensive patients^{20;21}. To our knowledge, only one study published in 1973 documented an increased prevalence of coronary heart disease in KSF²², and that result was not confirmed by others²³. Our study provides the first independent confirmation of an association between nephrolithiasis and coronary heart disease in a large-scale population, and also confirms an increased prevalence of stroke in KSF.

In this study, the associations between nephrolithiasis and hypertension, diabetes or CVD were only partly justified by the older age and higher BMI of KSF. The relations of hypertension with age and BMI are well documented in older age groups²⁴ and obese individuals²⁵. However, the O.R. for hypertension in our population with nephrolithiasis remained higher after adjusting the results for age and BMI, suggesting the existence of further risk factors.

Obesity is a known risk factor for diabetes and cardiovascular diseases²⁶, but in our study the association of nephrolithiasis with diabetes remains significant after adjustment for age and BMI. It is conceivable that the adverse effects of certain forms of treatment of kidney stone disease may result in an increased risk of diabetes and CVD. Thiazide diuretics are frequently used in the treatment of nephrolithiasis, and a possible association between low-dose thiazide diuretics and an enhanced risk of diabetes was recently reported by Taylor *et al.*²⁷. An increased risk of diabetes has also been documented in patients undergoing extracorporeal shock wave lithotripsy²⁸. However, only a minor proportion of patients in our population had been submitted to any form of treatment for nephrolithiasis, except for symptomatic treatment, and in

those who were treated no association was observed between treatment and the development of diabetes or CVD.

In our study, the age of the diagnosis of nephrolithiasis preceded the age of the diagnosis of diabetes and other cardiovascular outcomes, in most cases by several years. Even considering that the onset of type 2 diabetes may precede its clinical diagnosis by as much as seven years²⁹, kidney stone disease cannot be interpreted as a consequence of diabetes, as usually described in medical literature, but, instead, it appears to occur early in life in individuals with a greater predisposition for the future development of diabetes.

In the past, the search for an association between nephrolithiasis and coronary heart disease gave contradictory results^{22;23;30}. Our results document an association between nephrolithiasis and myocardial infarction later in life and, in women, nephrolithiasis remains an independent risk factor after adjustment for the presence of diabetes and hypertension.

Li *et al.*³¹ found a high percentage of cases with a history of kidney stones in patients with normal blood pressure who developed stroke over 6-year follow-up, but that difference did not reach statistical significance after adjustment for other risk factors. Our study confirms the association between nephrolithiasis and stroke and explains it by the higher prevalence of hypertension and diabetes observed in KSF.

Nephrolithiasis is gradually being recognized as a systemic disease indicative of an adverse metabolic environment^{32;33}. The differences in the ages of diagnosis of the different co-morbidities found in our study suggests that the causal mechanism may already be present when the lithogenic process began, and its identification should be part of a more comprehensive intervention in kidney stone prevention.

The results express the need for prospective long-term studies to assess the risk for CVD and diabetes in kidney stone disease and it is recommended to undertake a careful assessment of cardiovascular risk factors in stone forming patients.

Limitations:

The recognition of comorbidities was based on the knowledge that patients have about their own health status and we admit some bias related to the fact that individuals affected by one disease condition may have a greater probability of other conditions being diagnosed, simply by getting more medical attention. The operational definition of nephrolithiasis could not be compared with the concept used by the health professionals who made that diagnosis. It was not possible to identify any biochemical parameters related to nephrolithiasis or cardiovascular risk. The cross-sectional nature of the study did not allow a clear identification of a causal link between nephrolithiasis and the outcomes of interest.

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Conflict of interest statement:

None to declare.

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Captions and labels

Figure 1 – Distribution of kidney stone formers according to age.

Figure 2 – Mean age of appearance of symptoms from the chronic diseases under consideration. *= $p < 0.05$; **= $p < 0.001$.

Table 1 – Prevalence of chronic diseases associated with high cardiovascular risk in the studied population.

Table 1

Chronic disease	Overall (n = 23,349)	Non-stone formers (n = 21,648)	Stone formers (n = 1,701)	P value
Hypertension	30.2%	28.6%	50.4%	< 0.001
Obesity	17.3%	16.9%	22.7%	< 0.001
Diabetes	10.0%	9.4%	16.6%	< 0.001
Myocardial infarction	1.9%	1.8%	3.3%	< 0.001
Stroke	2.3%	2.1%	3.8%	< 0.001