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ORIGINAL PAPER

Increased 10-year cardiovascular disease and mortality risk scores in asymptomatic patients with calcium oxalate urolithiasis

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Abstract Both the prevalence of cardiovascular risk factors and event rate are increased in patients with urolithiasis. Screening is recommended to all patients who have high cardiovascular risk. The aim of this study was to document 10-year risk of cardiovascular disease and mortality in asymptomatic patients with urolithiasis. Consecutive 200 patients with calcium oxalate urolithiasis were compared with 200 age- and sex-matched healthy controls. Ten-year cardiovascular disease risk was calculated with the Framingham Risk Score and mortality risk with SCORE risk score. Calcium, oxalate, and citrate excretion were studied as urinary stone risk factors. The results indicate that patients with urolithiasis had higher total cholesterol ($p < 0.0001$), lower HDL-cholesterol ($p < 0.0001$), and higher systolic blood pressure ($p < 0.0001$) and hsCRP ($p < 0.0001$) compared with controls. Patients with urolithiasis had a higher Framingham Risk Scores [OR 8.36 (95% CI 3.81–18.65), $p = 0.0001$] and SCORE risk score [OR 3.02 (95% CI 1.30–7.02), $p = 0.0006$] compared with controls. The Framingham and SCORE risk score were significantly correlated with urinary calcium ($p = 0.0001$, $r = 0.460$, and $p = 0.005$, $r = 0.223$, respectively) and oxalate excretion ($p = 0.0001$, $r = 0.516$, $p = 0.001$, $r = 0.290$, respectively). In multiple linear regression analysis, urinary calcium and oxalate excretion, age, sex, total cholesterol, HDL-cholesterol, hsCRP and smoking were the independent predictors of 10-year cardiovascular disease risk and urinary calcium and oxalate excretion, age, sex, total cholesterol, fasting blood glucose for 10-year cardiovascular mortality. In conclusion, patients with calcium oxalate urolithiasis carry high risk of cardiovascular disease and mortality. All patients should be screened at the initial diagnosis of urolithiasis for the risk factors.

Keywords Urolithiasis · Calcium oxalate · Cardiovascular disease risk · Cardiovascular mortality risk

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Introduction

Urolithiasis and coronary artery disease are disorders increasing in prevalence throughout the world [1, 2]. Both epidemiological and etiological associations have been documented in various studies. The metabolic syndrome is the sum of the well-known cardiovascular risk factors such as abdominal obesity, insulin resistance ± glucose intolerance, raised blood pressure and dyslipidemia. Numerous studies have documented an increase in the prevalence of urolithiasis with obesity, diabetes mellitus and hypertension [3–5]. Metabolic syndrome by itself is also a prone condition for the development of urolithiasis [6].

Increased risk of cardiovascular diseases has also been shown in patients with urolithiasis. History of urolithiasis was associated with increased risk of myocardial infarction; angina and coronary artery bypass grafting [7]. Documentation of cardiovascular risk in asymptomatic individuals helps to direct future interventions in early period and plays an important role in the prevention of

disease development. Global risk scores such as the Framingham Risk Score etc. are the recommended screening tools for the assessment of cardiovascular risk [8]. The aim of this study was to assess 10-year cardiovascular disease and mortality risk in asymptomatic patients with calcium oxalate (CaOx) urolithiasis without a clinical history of coronary heart disease.

Materials and methods

Subjects

The cases comprised 200 consecutive patients with CaOx stone disease, aged 18–80 years selected from outpatient urology clinic of our institution. All patients were evaluated and treated appropriately for their urinary calculi. Patients were asymptomatic for cardiovascular diseases at the time of recruitment and any history of previous cardiovascular event was excluded. Patients who had end stage diseases such as renal, hepatic or heart failure, active cancer treatment, on steroid, diuretic or vitamin/mineral supplement therapy and history of conditions predisposing to calcium-based stone formation (e.g., hyperparathyroidism, renal tubular acidosis, sarcoidosis, inflammatory bowel disease) were not included into study.

The controls were 200 age- and sex-matched subjects recruited among 400 individuals who visited our hospital for an annual check-up and had not been observed any acute or chronic systemic diseases. Each subject was screened by clinical history, thorough physical examination, and routine chemical analysis for the evidence of any disease. Subjects with history or evidence of any chronic systemic disease, pregnancy or a history of heavy smoking, drug, or alcohol abuse were excluded. Patients taking or on treatment with any drug that can interfere with study parameters prior to the start of study were also not included. None of the subjects had a history of urinary stone disease. Abdominal ultrasonography which is a normal part of check-up program did not reveal urinary stone in any of the control subjects. They had no history of predisposing diseases for renal stone formation.

Study design

This was a single center, cross-sectional, case control study conducted at Yeditepe University Hospital from June 2009 to June 2010 in accordance with Good Clinical Practice and the ethical principles of the Declaration of Helsinki. Written informed consent was obtained from each study subjects. All study documentation was reviewed and approved by the Institutional Review Board.

Objectives

The primary objective was to determine whether patients with CaOx renal stone disease had higher risk of 10-year cardiovascular disease and 10-year mortality from cardiovascular diseases. Secondary objectives were their association with stone forming risk factors in 24-h urine samples, fasting blood glucose (FBG) levels, urine pH, and hsCRP.

Measurements

Ten-year risk for development of coronary heart disease

The Framingham risk-scoring table was used for calculating the 10-year risk for developing coronary heart disease [9]. The risk factors included into the scale were age, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), systolic blood pressure (SBP), hypertension whether treated or not, and cigarette smoking. The total score was yielded with the sum of points for each risk factor using the gender-specific tables. The risk of the probability of experiencing a cardiac event over a 10-year period was defined in terms of three categories (low: <10%; intermediate: 10–20% and high >20%).

Ten-year risk for development of fatal cardiovascular disease

SCORE (Systematic COronary Risk Evaluation) risk charts for populations at low cardiovascular disease risk based on total cholesterol were used for estimation of 10-year risk of fatal cardiovascular disease in subjects [10]. The risk factors used for calculations included sex, age, TC, SBP, hypertension, and cigarette smoking. Points obtained from the gender-specific tables for each risk factor are summed to yield the total score. The risk was defined in terms of escalating categories (<1, 1, 2, 3–4, 5–9, 10–14, 15% and over) on the basis of the probability of having fatal cardiovascular disease over a 10-year period.

Laboratory measurements

All blood samples were taken after 12 h fasting in the morning. Serum glucose levels were analyzed with the glucoxidase method. Serum total cholesterol and HDL-cholesterol were measured by enzymatic colorimetric assays (Roche Diagnostics GmbH, Mannheim, Germany) and hsCRP by an immunoturbidimetric assay (Roche Diagnostics GmbH, Mannheim, Germany).

Blood pressure and anthropometric measurements

Blood pressure was measured from the right upper extremity using a mercury sphygmomanometer with the patient in a sitting position. After 10 min of rest, the

average of three consecutive measurements was accepted as the systolic blood pressure value.

Body weight was measured with light dress on fasting and height on barefoot. Body mass index was calculated with formula of BMI = Body weight (kg)/height (m^2).

The risk factors for renal stone disease

Stone forming risk factors have been assessed in 24-h collected urine of each patient in specially prepared bottles obtained from the laboratory. Urine collections were preserved with thymol in isopropanol and kept refrigerated at 4°C during collection. Samples were acidified to adjust the pH to 1.5–2 with 6 M HCl (approximately 10 mL HCl/24-h sample based on normal adult output of 1,000–2,000 mL/24 h to ensure complete dissolution of any CaOx crystals formed and to prevent spontaneous conversion of ascorbate into oxalate and kept below −20°C until evaluation. The analysis of the urine specimen included the assessment of the urinary risk factors; namely, oxalate, calcium, and citrate. Urinary citrate was assessed enzymatically (citrate lyase); urinary oxalate was determined by ion chromatography; and calcium using atomic absorption method. To ensure complete urine collection in an individual basis, daily urine collection was based on the normal range of creatinine contents of urines in men and women. No specific diet program was ordered to patients prior to urine collection. The 24-h urine output values were recorded in each patient.

Statistics

Statistical data were analyzed by SPSS® 15.0 for Windows®. Descriptive statistics were provided for each variable including demographic, laboratory, and blood pressure measurements. Kolmogorov–Smirnov test was used for testing normality. Parametric tests used as variables were normally distributed. Results are shown as mean ± SD. Odds ratios were calculated with contingency table analysis with 95% confidence intervals. Comparisons between patients and controls were done using paired samples Student's *t* test and unpaired samples Student's *t* test for comparisons between men and women. Pearson test was used for correlation analysis. Stepwise multiple regression analysis was used to determine independent predictors of the Framingham and SCORE risk scores. Statistical significance was considered at $p < 0.05$.

Results

Demographic data

Study subjects were predominantly male. Of 200 patients, 135 (67.5%) of them were men. Mean age of the subjects was 43±12 years with a range of 19–67 years. The controls were age-matched. There was no age difference between men and women. Majority of the patients were below the age of 45 years (54% of men and 62% of women). Body mass index (BMI) was higher in men than in women, both in patients and controls (26.8 ± 3.4 vs. 24.6 ± 2.7 in controls and 27.3 ± 2.9 vs. 24.4 ± 3.4 in patient, respectively, $p = 0.02$). There was no statistically significant difference in BMI among patients and controls either in women or men.

Cardiovascular risk factors

Cardiovascular risk factors of the study subjects were presented in Table 1. Patients with urolithiasis had higher TC ($p < 0.0001$), lower HDL-C ($p < 0.0001$), and higher SBP ($p < 0.0001$) and higher FBG ($p = 0.01$) compared with controls. The rate of cigarette smoking was found to be higher in patients than in controls ($p < 0.0001$). hsCRP levels were significantly higher in patients with urolithiasis compared with controls both in men and women ($p < 0.0001$). Men had similar hsCRP levels as women.

Patients with urolithiasis had a higher Framingham Risk Score compared with controls with an odds ratio of 8.36 (95% CI 3.81–18.65, $p = 0.0001$). Women had higher risk compared to men [9.24 (95% CI 1.11–76.77), $p = 0.016$ vs. 7.64 (95% CI 3.37–17.33), $p = 0.0001$].

The SCORE risk score was also found to be higher in patients with urolithiasis. Odds ratio of total group for mortality risk was 3.02 (95% CI 1.30–7.02, $p = 0.0006$). It was 3.08 (95% CI 1.23–7.66, $p = 0.01$) for men, but was not statistically significant in women [3.12 (95% CI 0.31–31.00, $p = 0,309$)].

Urinary stone risk factors

Except urine pH, all urinary risk factors were found to be higher in men compared to women. Most of the urine chemistry analyses were within normal laboratory range. Hyperoxaluria was observed in 25/108 of the patients (21 men and 4 women). Hypercalciuria above 320 mg/day was observed in 17/108 patients (11 men and 6 women).

Correlations

Ten-year cardiovascular disease and mortality risk were positively correlated with urinary stone risk factors (Fig. 1a–d), except urine pH. Urinary citrate excretion did not correlate with SCORE risk factor. The Framingham Risk Score was also significantly correlated with age ($p = 0.0001$, $r = 0.603$), male sex ($p = 0.0001$, $r = 0.313$), TC ($p = 0.0001$, $r = 0.375$), HDL-C ($p = 0.0001$, $r = -0.348$), cigarette smoking ($p = 0.0001$, $r = 0.355$), FBG ($p = 0.001$, $r = 0.268$) and SBP ($p = 0.0001$, $r = 0.463$).

Table 1 Cardiovascular risk factors of study subjects

	Patients ($n = 200$)	Controls ($n = 200$)	p
Age (years)	43 ± 12	43 ± 12	0.549
Total cholesterol (mg/dl)	221.9 ± 42.7	202.6 ± 30.5	<0.0001
HDL-cholesterol (mg/dl)	43.2 ± 9.0	53.75 ± 16.6	<0.0001
Fasting blood glucose (mg/dl)	103.3 ± 19.4	98.56 ± 10.34	0.01
hsCRP (mg/l)	2.68 ± 1.55	1.43 ± 0.78	<0.0001
Cigarette smoking (%)	35	25	0.266
Systolic blood pressure (mmHg)	128.1 ± 16.4	113.0 ± 12.7	<0.0001
Framingham Risk Score	9.0 ± 9.3	3.8 ± 3.9	<0.0001
SCORE risk score	1.2 ± 2.4	0.5 ± 0.9	<0.0001

Results presented here were mean ± SD except smoking which was ratio

The SCORE risk score was correlated with age ($p = 0.0001$, $r = 0.637$), male sex ($p = 0.028$, $r = 0.173$), TC ($p = 0.0001$, $r = 0.293$), FBG ($p = 0.001$, $r = 0.332$) and SBP ($p = 0.0001$, $r = 0.372$). Neither of the scores was correlated with body mass index.

Urinary calcium excretion was found to be correlated with age ($p = 0.003$, $r = 0.233$), TC ($p = 0.014$, $r = 0.194$), SBP ($p = 0.029$, $r = 0.172$) and cigarette smoking ($p = 0.007, r = 0.211$). Urinary oxalate excretion was found to be correlated with age ($p = 0.0001, r = 0.400$), male sex ($p = 0.025$, $r = 0.176$), HDL-C ($p = 0.026$, $r = -0.175$), cigarette smoking (0.002, $r = 0.237$), FBG ($p = 0.028$, $r = 0.174$), and SBP ($p = 0.0001$, $r = 0.299$). Urinary citrate excretion correlated only with hsCRP ($p = 0.022, r = -0.180$). There was no correlation between BMI and any urine stone forming risk factors.

Highly sensitive C-reactive protein levels was correlated with the Framingham Risk Score ($p = 0.0001, r = 0.363$), the SCORE risk score ($p = 0.01$, $r = 0.186$), urinary oxalate excretion ($p = 0.001$, $r = 0.254$), age ($p = 0.0001$, $r = 0.277$), cigarette smoking ($p = 0.004$, $r = 0.225$), and SBP ($p = 0.001, r = 0.266$).

A stepwise multiple linear regression analysis was performed to assess the independent determinants of 10-year cardiovascular disease and mortality risk in patients with urolithiasis. The Framingham or SCORE risk score was selected as dependent variables in the model. Independent variables were urinary stone risk factors (urinary calcium, oxalate and citrate excretion, and urine pH), each parameter that was used for the calculation of cardiovascular risk scores (age, sex, TC, HDL-C, SBP, cigarette smoking), FBG and hsCRP. Results were summarized in Tables 2 and 3.

Discussion

The presence of urolithiasis was independently associated with a higher 10-year risk of cardiovascular disease and mortality in this study. These data suggest that cardiovascular risk was associated with some of the urinary stone risk factors and this association persisted after controlling for multiple potential confounders. These findings are consistent with some previous studies that have reported increased cardiovascular events in patients with urolithiasis [7, 11, 12].

Urolithiasis is not a disease localized solely to kidneys, but has many systemic consequences. It was documented in many epidemiological studies that increased risk of kidney stone formation was independently associated with systemic diseases such as obesity [3], diabetes mellitus [13], hypertension [14] and metabolic syndrome [15]. There are many similarities between urolithiasis and metabolic syndrome. First of all, global prevalence of both conditions increases in time and are more common in industrialized countries [16]. Age distribution of urolithiasis [17] is similar to metabolic syndrome and common in adults with age between 20 and 70 years [18]. In addition, increased risk of urolithiasis was reported in diseases that constitute metabolic syndrome [3, 13, 14]. Both the prevalence of metabolic syndrome [19] and urolithiasis [3] increases with body weight. Our results are consistent with previous studies in that higher TC, SBP, FBG lower HDL-C were observed in patients with urolithiasis. FBG level exceeded the limit of diabetes diagnosis of 126 mg/dl in 13 (26%) of the patients and the limit of hypertension of 140 mmHg in 20 (40%) of the patients in contrast to controls in which none of the subjects exceeded the limits.

Increased risk of cardiovascular diseases is a well-known sequela of metabolic syndrome and related disorders. Any disease that has an association with metabolic syndrome but not a component of it such as polycystic ovary syndrome, nonalcoholic fatty liver disease etc. has increase in cardiovascular disease risk [20, 21]. Although individuals with myocardial infarction did not have a higher prevalence of renal stone than expected [22], in the Health Professionals Follow-up Study, history of kidney

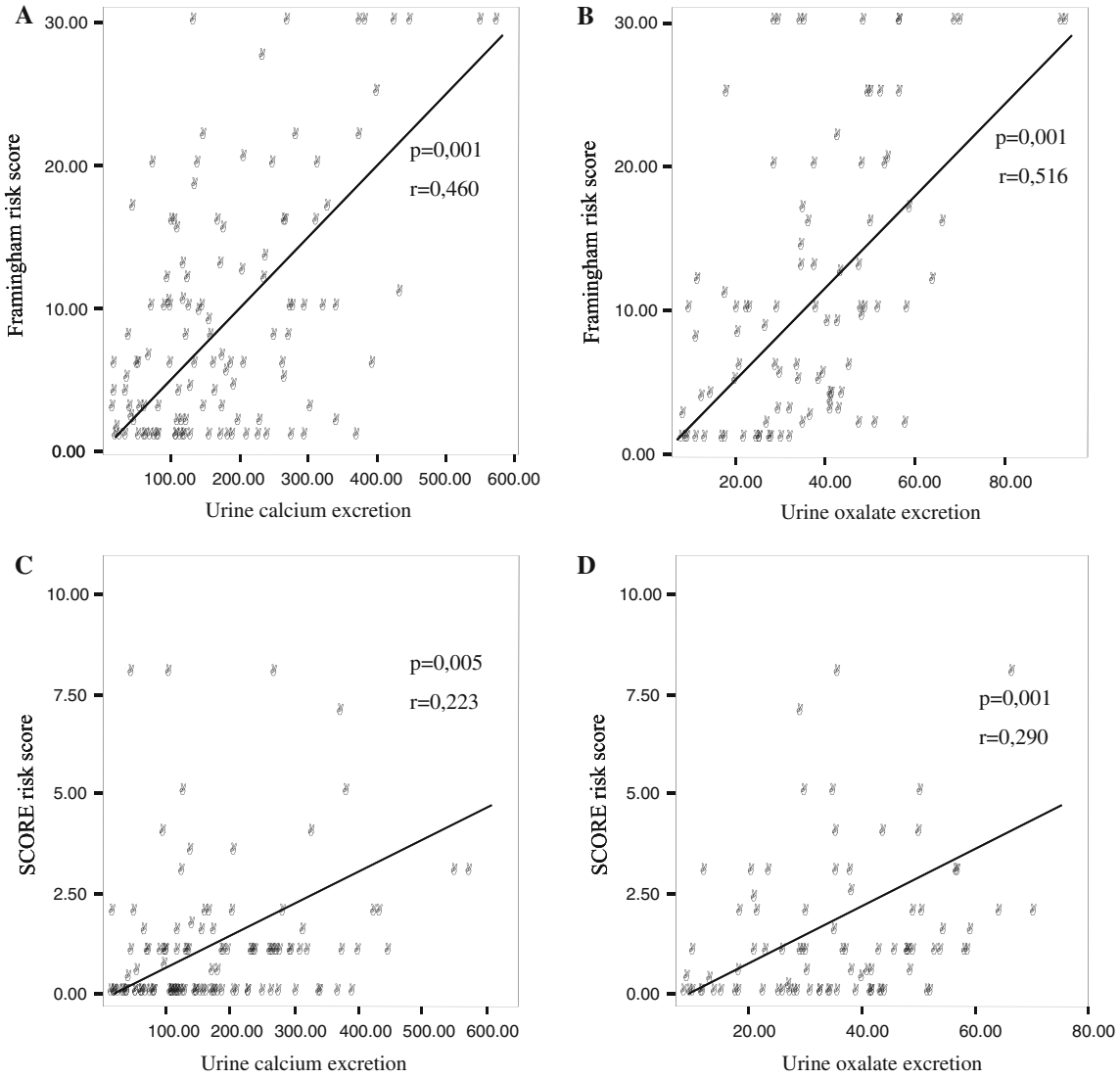

Fig. 1 Correlation of 10-year cardiovascular disease and mortality risk with urine stone risk factors. The Framingham and SCORE risk scores were positively correlated with both urinary calcium (**a** and **c**, respectively) and oxalate excretion (**b** and **d**, respectively)

stones was associated with 16% increased risk of myocardial infarction, 27% increased risk of angina and 15% increased risk of coronary artery bypass grafting [7]. In Portuguese National Health Survey, among 23,349 individuals, the prevalence of kidney stone disease was 7.3% and myocardial infarction and stroke were 1.3 times more prevalent in kidney stone formers [12]. Since many of the patients are asymptomatic for cardiovascular diseases at the diagnosis of urolithiasis, screening may help us to determine patients at risk at an early period. The American College of Cardiology Foundation (ACCF) and the American Heart Association (AHA) recently published their latest task force guideline for the assessment of cardiovascular risk in asymptomatic adults and recommended global risk scores (such as the Framingham Risk Score) to be obtained for risk assessment in all asymptomatic adults without a clinical history of coronary heart disease [8]. Parallel to these statements, our results of increased cardiovascular disease and mortality risk in asymptomatic urolithiasis patients entail risk assessment in this group absolutely necessary. These simple and inexpensive tests help us to determine subsequent strategies to be undertaken and target preventive strategies. Individuals at low-risk do not require further testing for risk assessment and intermediate and high-risk patients require intensive preventive interventions.

Besides co-incidence of urolithiasis and cardiovascular diseases and risk factors in epidemiological manner, there are some etiological similarities too. The development of cardiovascular diseases is closely linked to chronic systemic inflammation. Many systemic inflammatory markers were found to be elevated in atherosclerosis [23] and most

Table 2 Stepwise multiple regression analysis for variables with the Framingham Risk Score in patients with urolithiasis

	B[a]	Beta[b]	95% CI of B	*p*
Independent variables				
Urinary calcium excretion	0.040	0.460	0.028–0.052	0.0001
Urinary oxalate excretion	0.231	0.426	0.162–0.395	0.0001
Age	0.309	0.428	0.223–0.395	0.0001
Sex	−4.552	−0.230	−6.605 to −2.449	0.0001
Total cholesterol	0.049	0.223	0.027–0.070	0.0001
HDL-cholesterol	−0.166	−0.161	−0.266 to −0.066	0.001
Cigarette smoking	−5.141	−0.276	−6.824 to −3.457	0.0001
hsCRP	0.749	0.125	0.208–1.290	0.007
Excluded variables				
Systolic blood pressure		0.096		0.059
Fasting blood glucose		0.112		0.089
Urine pH		0.038		1.0
Urinary citrate excretion		0.120		0.061

Multiple coefficient of determination (R^2) = 0.707, $p = 0.0001$

[a] Unstandardized regression coefficient

[b] Standardized coefficient

Table 3 Stepwise multiple regression analysis for variables with the SCORE risk score in patients with urolithiasis

	B[a]	Beta[b]	95% CI of B	*p*
Independent variables				
Urinary calcium excretion	0.004	0.161	0.000–0.007	0.042
Urinary oxalate excretion	0.047	0.328	0.026–0.068	0.0001
Age	0.120	0.637	0.097–0.143	0.0001
Sex	−0.741	−0.144	−1.356 to −0.126	0.0001
Total cholesterol	0.011	0.193	0.004–0.018	0.0001
Fasting blood glucose	0.019	0.155	0.005–0.034	0.011
Excluded variables				
Systolic blood pressure		0.091		0.156
HDL-cholesterol		−0.006		0.926
Urine pH		0.027		0.641
Urinary citrate excretion		0.051		0.068
Cigarette smoking		−0.035		0.540
hsCRP		0.010		0.872

Multiple coefficient of determination (R^2) = 0.472, $p = 0.01$

[a] Unstandardized regression coefficient

[b] Standardized coefficient

of them are also involved in the pathogenesis and progression of urolithiasis [24]. Higher levels of hsCRP in patients with urolithiasis and correlation with urinary stone risk factors and cardiovascular risk scores in our study are in accordance with above mentioned results.

Low urinary citrate excretion is accepted as a predisposal condition for the formation of calcium oxalate stones. In their studies, Cupisti et al. [25] demonstrated that low urinary citrate excretion in calcium stone formers was associated with insulin resistance. It was not possible to detect insulin resistance in our study, but urinary citrate excretion was significantly and negatively correlated with the Framingham Risk Score. This may indicate the possible role of lower citrate excretion on cardiovascular risk.

Many stone forming risk factors have been shown to correlate with body weight and prevalence of stone disease was increased in obese subjects [26, 27]. Another well-known data is that cardiovascular as well as all-cause mortality is increased in obese subjects [28]. Any condition that is related to increase in body weight is expected to

have an increase in cardiovascular risk. But interestingly, we did not observe any relationship of BMI with urinary solute excretion or cardiovascular risk scores. This may be due to low number of obese (BMI >30 kg/m^2) subjects and relatively young age of the patients. On the other hand, this may also be an important finding that shows us the increase in cardiovascular risk in patients with urolithiasis may not be due to higher BMI in these subjects. If this is true, it strengthens the relationship between urinary oxalate excretion and cardiovascular risk. Nevertheless, abdominal obesity is more important than simple obesity to define the cardiovascular risk. Waist circumference better reflects visceral obesity than body mass index. Lack of correlation between BMI and cardiovascular risk scores in this study does not mean that they are not related to visceral obesity. Since we could not get waist circumference measurements of the subjects, it will not be possible to answer this question.

Relatively small sample size to draw a constant conclusion, lack of the assessment of nutritional, social and economical status and insulin resistance were the main limitations of this study. Selection of healthy individuals attending for annual check-ups might create a bias in the control group since they might be healthier than average population. The follow-up of these patients in a prospective manner for the development of cardiovascular diseases will provide better results.

In conclusion, asymptomatic patients with calcium oxalate stone disease have an increased risk of 10-year cardiovascular disease and mortality risk. All kidney stone formers should be screened for cardiovascular risk factors very carefully.

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Conflict of interest The authors have nothing to disclose.

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