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ORIGINAL PAPER

Updated epidemiologic study of urolithiasis in Turkey II: role of metabolic syndrome components on urolithiasis

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Abstract The components of metabolic syndrome, such as obesity, hypertension, and diabetes, are thought to be associated with urolithiasis. However, there are few large-scale studies that have examined the association between metabolic syndrome and urolithiasis, which prompted us to study and evaluate the relationship between metabolic syndrome components and urolithiasis in a nationwide survey, using the cross-sectional study conducted by a professional investigation company, with 2,468 enrolled participants, aged between 18 and 70 years, from 33 provinces in Turkey. Participants were interviewed face-to-face by medical faculty students. Participants with a history of urolithiasis (Group 1) were compared with participants without a history of urolithiasis (Group 2) in terms of hypertension, diabetes, body-mass index (BMI), waist size, and trouser size using Chi-square and odds ratio tests. Of the 2,468 participants, 274 (11.1%) reported a history of urinary stone disease diagnosed by a physician. The percentage of participants with hypertension along with urolithiasis was significantly higher than that in participants without urolithiasis (16.9 and 34.3%, *p* 0.000, OR 3.0). The percentage of participants with diabetes in groups 1 and 2 was 14.2 and 9%, respectively (*p* 0.001, OR 1.83). The mean BMI was 27.2 and 25.2, respectively (*p* 0.01). Participants with a BMI >30 had a 2.2-fold increased risk of having urolithiasis. The mean waist size was significantly greater in participants with urolithiasis (*p* 0.000). Those with a waist size >100 cm had a 1.87-fold increased risk of having urolithiasis. The mean trouser size was also significantly larger in those participants who were stone formers (*p* 0.003). The results indicate that metabolic syndrome components are important factors in the development of urolithiasis.

Keywords Epidemiology · Metabolic syndrome · Obesity · Urolithiasis · Urinary stone disease

Introduction

The prevalence of urolithiasis ranges from 2 to 20% throughout the world based on the geographic and socioeconomic characteristics of the different populations [1], and more than $2 billion is spent on treatment each year [2, 3]. The worldwide prevalence of the disease appears to have increased in the last quarter of the twentieth century for both men and women [4, 5]. The identification of common, modifiable risk factors for kidney stones may result in new approaches to the treatment and prevention of urolithiasis.

An increasing percentage of the population is affected by obesity and metabolic syndrome. Metabolic syndrome is a condition characterized by insulin resistance, and it is clinically defined by the clustering of abdominal obesity, dyslipidemia, elevated blood pressure, and elevated fasting plasma glucose [6–8]. For many years, there were few data concerning the relationship between metabolic syndrome and the risk of developing renal diseases. However, recent epidemiological analyses have found that patients with metabolic syndrome are at high risk for chronic kidney diseases [9–12].

Insulin resistance, the fundamental risk factor for metabolic syndrome and diabetes mellitus, results in defective renal ammoniagenesis and a low urine pH. A low urine pH is the major lithogenic factor in idiopathic uric acid nephrolithiasis and may result in the production of uric acid

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stones [13]. Pak et al. [14] showed that the proportion of uric asid (UA) stones was especially high (33.9%) among stone formers with type 2 diabetes. However, the diabetics in this study also were obese. Differentiating the effects of obesity and type 2 diabetes on stone formation, then, could not be established.

Some authors have argued that the perturbations of calcium metabolism may possibly be linked to the development of both kidney stone disease and hypertension. Hypercalciuria is the predominant metabolic abnormality in subjects with calcium nephrolithiasis, and there may be a link between the formation of kidney stones and the development of hypertension.

To evaluate the correlation of urolithiasis with these common public health problems, we conducted a nationwide, population-based, cross-sectional study.

Materials and methods

A sample consisting of 2,468 randomly selected individuals between 18 and 70 years of age from 33 provinces in Turkey enrolled in a cross-sectional study conducted by A&G, a professional marketing investigation company. The population was representative of Turkey in its demographic and socioeconomic properties according to the State Institute of Statistics.

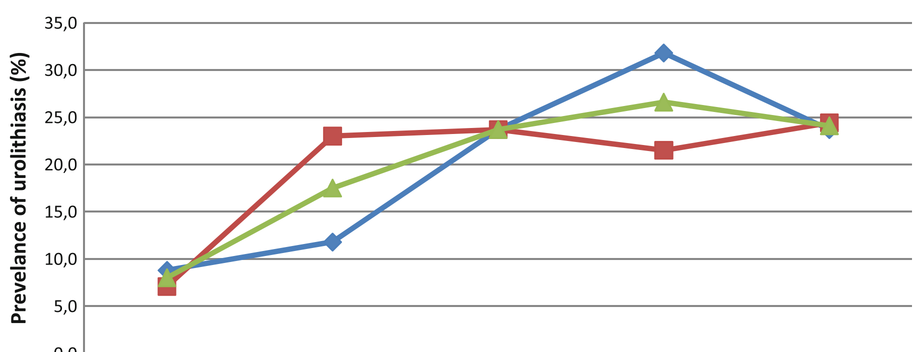
The study was designed in two parts. The aim of the first part of the study was to evaluate the epidemiological characteristics of urolithiasis in Turkey [15]. The aim of the second part of the study was to analyze the relationship between metabolic syndrome components and urolithiasis. The interviewers were trained in how to complete the questionnaire before the survey was begun. The height, weight, and waist circumference measurements were completed by a single certified urologist. Using a specially designed questionnaire, participants were interviewed face-to-face at their homes. In the second part of the survey, the participants were asked whether they had been diagnosed with diabetes mellitus or hypertension by a physician. The interviewers also measured the height, weight, and waist circumference of the participants. The diagnosis of either diabetes or hypertension was accepted only when the patient was under the care of a physician for the disorders. Participants were questioned concerning their dietary habits, such as the consumption of water, soft drinks, milk, coffee, tea, meat, fish, or vegetables.

Participants who had experienced spontaneous stone passage, had a procedure for urolithiasis including shock wave lithotripsy, or whose stones were radiologically visible at the time of clinical symptoms were defined as "definitive urolithiasis". Participants who had a past history of renal colic without a physician's diagnosis were defined as "possible urolithiasis." Participants with definitive urolithiasis were evaluated concerning the relationship of urolithiasis to other factors.

Analyses were completed using Chi-square tests. Odds ratios (OR) were calculated. Statistical determinations were within the 95% confidence interval (CI). All p values were two-tailed, and $p < 0.05$ was considered statistically significant. The data were analyzed with an SPSS^{TM} (SPSS version 13.0, Chicago, IL) statistical software package.

Results

Of the 2,468 participants, 274 (11.1%) reported a history of definitive urolithiasis and 52 (2.1%) had possible urolithiasis. The prevalence rates of urolithiasis in Turkey increased gradually with age in both men and women (Fig. 1). The male to female ratio was 1:1 (Table 1). The average cumulative recurrence rate of urolithiasis was 16.7% after 1 year and 35.7% after 5 years.



	<24 years age	25-34 years age	35-44 years age	45-54 years age	55-70 years age
Male	8,8	11,8	23,7	31,8	23,7
Female	7,1	23,0	23,7	21,5	24,4
Overall	8,0	17,5	23,7	26,6	24,1

Fig. 1 Age-related prevalence rates of urolithiasis in men and women

Body Mass Index (BMI) was significantly related to the risk of urolithiasis. Overall, participants with a BMI over 30 increased their risk of urolithiasis by 2.23-fold when compared with participants with a BMI <30 (Table 2). The presence of obesity increased the risk of urolithiasis in both men (p 0.000, OR 2.68) and women (p 0.002, OR 1.91). Increased waist circumference (WC) also increased the risk of urolithiasis (p 0.000, OR 1.59). However, when WC was calculated separately for men and women, abdominally obese men (WC $\geq$ 102 cm) had a higher risk of urolithiasis (p 0.000, OR 2.11), but abdominally obese women (WC $\geq$ 89 cm) did not (p 0.14) (Table 3).

Of the participants involved in the survey, 223 had been diagnosed with diabetes mellitus and 417 with hypertension. The prevalence of urolithiasis in diabetics was 17.4%, and in non-diabetics it was 10.4% (p 0.001, OR 1.81). Diabetes increased the risk of urolithiasis in both men and women (Table 4). Hypertension also significantly increased the risk of urolithiasis when compared with normotensive individuals (p 0.000, OR 3.0) (Table 5).

Multi-variant analysis revealed that only hypertension and obesity had significant impacts on the development of urolithiasis (p 0.000 and 0.03, respectively). The calculated OR was 2.58 (CI: 1.52–3.48) for hypertension and 1.65 (CI: 1.19–2.3) for obesity.

The dietary habits of the obese participants were analyzed. Among the obese participants, those who regularly consumed more than 1 glass daily of acidic soft drinks

Table 1 Demographic characteristics of the participants

n 2,468	
Mean BMI (kg/m^2): 25.5 ± 4.6 (range 15–50)	
Presence of hypertension: 417 (16.8%)	
Presence of diabetes mellitus: 223 (9%)	
Participants with urolithiasis:	
Definitive: 274 (11.2%)	
Possible: 52 (2.1%)	
Prevalence	
Men: 135 (10.9%)	
Women: 139 (11.2%)	
Incidence	
Men: 18 (1.4%)	
Women: 24 (1.9%)	

Table 2 Correlation of Body Mass Index (BMI, kg/m^2) and presence of urolithiasis

BMI	Subjects w/o stone	Subjects with stone	p	Odds ratio	CI
Overall					
<30	1,887 (86%)	201 (73.4%)	0.000	2.23	1.66–3.0
≥30	307 (14%)	73 (26.6%)			
For Men					
<30	974 (88.5%)	100 (74.1%)	0.000	2.68	1.75–4.11
≥30	127 (11.5%)	35 (25.9%)			
For Women					
<30	913 (83.5%)	101 (72.7%)	0.002	1.91	1.27–2.86
≥30	180 (16.5%)	38 (27.3%)			

CI Confidence Interval

Table 4 Relation of urinary stone disease with diabetes mellitus

	Subjects w/o stone	Subjects with stone	p	Odds ratio	CI (95%)
Overall					
DM (+)	184 (8.4%)	39 (14.2%)	0.001	1.81	1.25–2.62
DM (−)	2,010 (91.6%)	235 (85.8%)			
For Men					
DM (+)	70 (6.4%)	16 (11.9%)	0.029	1.98	1.11–3.52
DM (−)	1,031 (93.6%)	119 (88.1%)			
For Women					
DM (+)	114 (10.4%)	23 (16.5%)	0.03	1.7	1.04–2.77
DM (−)	979 (89.6%)	116 (83.5%)			

DM Diabetes Mellitus, *CI* Confidence Interval

Table 3 The association between waist circumference and urinary stone disease

WC	Subjects w/o stone	Subjects with stone	p	Odds ratio	CI
Overall					
Abdominal Obesity (+)	915 (41.7%)	146 (53.3%)	0.000	1.59	1.24–2.05
Abdominal Obesity (−)	1,279 (58.3%)	128 (46.7%)			
For Men					
<102 cm	831 (75.5%)	80 (59.3%)	0.000	2.11	1.46–3.06
≥102 cm	270 (24.5%)	55 (40.7%)			
For Women					
<89 cm	448 (41%)	48 (34.5%)	0.14	–	
≥89 cm	645 (59%)	91 (65.5%)			

WC waist circumference, *CI* Confidence Interval

Table 5 Relation of urinary stone disease with hypertension

	Subjects w/o stone	Subjects with stone	p	Odds ratio	CI (95%)
Overall					
HT (+)	323 (14.7%)	94 (34.3%)	0.000	3.02	2.29–3.98
HT (−)	1,871 (85.3%)	180 (65.7%)			
For Men					
HT (+)	124 (11.3%)	42 (31.1%)	0.000	3.56	2.36–5.36
HT (−)	977 (88.7%)	93 (68.9%)			
For Women					
HT (+)	199 (18.2%)	52 (37.4%)	0.000	2.69	1.84–3.91
HT (–)	894 (81.8%)	87 (62.6%)			

HT Hypertension, *CI* Confidence Interval

(especially coke or similar beverages) had 2.8 times the possibility of having urolithiasis (p 0.01; CI 95%: 1.3–6.1).

Discussion

The predominant risk factors for metabolic syndrome appear to be abdominal obesity and insulin resistance. There is no doubt that insulin resistance predisposes the individual to the hyperglycemia of type 2 diabetes mellitus. There are some people who are not obese by traditional measures but are still insulin resistant with an increased number of metabolic risk factors. Although insulin-resistant individuals need not be clinically obese, they often have an abnormal distribution of fat that is predominantly characterized by upper body fat [16]. Because upper body obesity may result in insulin resistance in otherwise normal weight individuals, we analyzed our data for BMI and waist circumference as separate entities. Our results showed that the number of individuals with a waist circumference of over 100 cm (n 634, 25.7%) was greater than the number of individuals with a BMI of over 30 (n 380, 15.4%).

The risk of renal stone formation rises with an increase in body size. There are several prospective studies that have shown the relationship between obesity and the risk of kidney stone formation [17, 18]. Curhan et al. demonstrated a relationship between obesity and nephrolithiasis by combining data collected from the Nurses Health Study II and the HPFS. The cross-sectional analysis found a significant correlation between BMI and a history of kidney stones: OR = 1.38 for men and 1.76 for women with BMI >32 versus BMI <21 kg/m^2 [17, 18]. In our study, the OR was 3.53 for men and 2.39 for women with BMI >30 versus BMI <25 kg/m^2. As with BMI, waist circumference also showed a significant correlation with the risk of urinary stone disease. The calculated OR was 2.09 for men and 1.51 for women with waist circumference of 102 and 94, respectively. The exact mechanism of increased stone risk in obese individuals has not been fully elucidated. A number of mechanisms have been postulated, including increased dietary consumption, hyperinsulinemia, insulin resistance, and hyperuricemia. Although the association between body weight and calcium nephrolithiasis has not been clearly established, uric acid and infectious stones are both linked with increased body weight as well as insulin resistance. Recently, Sarica et al. prospectively compared the 24 h urinary stone risk factors from a group of obese patients followed in an endocrine clinic with those of a group of non-obese, non-stone formers. They showed that an increased body size increased the excretion of urinary stone-forming risk factors such as oxalate, calcium, and citrate [19]. A retrospective study in obese stone formers demonstrated that approximately 60% of stones analyzed were uric acid stones. Approximately half of these patients also had metabolic abnormalities, such as gouty diathesis, hypocitraturia, and hyperuricosuria, at levels that were significantly higher than those of non-obese stone formers [20]. Urine pH is one of the important factors in the pathogenesis of urinary stone disease. Siener et al. [21] evaluated the relationship between BMI and 24 h urine parameters in a population of idiopathic CaOx stone formers and found that an increased BMI was strongly associated with an increase in the excretion of stone promoters but not inhibitors. Although our study showed a strong association between body weight (BMI and waist circumference) and urinary stone disease, one of the limitations of our research is the lack of the identification of kidney stone type.

Although several studies have shown an increased risk of nephrolithiasis in obese individuals—and virtually all type 2 diabetics are overweight [16]—few epidemiological studies to date have examined the correlation between diabetes and nephrolithiasis. In their prospective study involving three large cohorts of male and female health professionals in the United States, Taylor et al. [22] showed a higher prevalence of a past history of kidney stones and a higher incidence of stone episodes among diabetic patients than among non-diabetic patients. This association was independent of age and BMI. The cross-sectional study conducted by Meydan et al. compared the prevalence of kidney stone disease between diabetic and age-matched non-diabetic subjects. Diabetic individuals had a significantly higher prevalence of nephrolithiasis (21% among 321 vs. 8% among 115) [23]. Lieske et al. [24], in a case–control community-based study, compared 3,561 stone formers with 3,561 age and gender-matched control subjects to show the relationship between urolithiasis and diabetes. Their results showed that a higher proportion of stone formers were diabetic and that stone formers had a 22% increased risk of being diabetic.

The frequency of diabetes was much higher in patients with uric acid nephrolithiasis. Daudon et al. [25] analyzed the main stone components in a series of 2,464 calculi. They found that the proportion of UA stones was 35.7% in patients with diabetes and 11.3% in non-diabetic patients. Stepwise regression analysis identified diabetes as the strongest factor that was independently associated with the risk for UA nephrolithiasis. Our results also showed a significant association between urolithiasis and diabetes (OR = 1.83, 95% = 1.25–2.62).

Research conducted by Tibblin et al. [26] in Sweden in 1967 was the first study to suggest an association between hypertension and nephrolithiasis. When the middle-aged men in this study were stratified according to blood pressure, the subjects with the highest blood pressure had the highest prevalence of urolithiasis. A larger cross-sectional study by Cappuccio et al. [27] showed the relationship between hypertension and nephrolithiasis. They found that hypertensive men had an age-adjusted odds ratio (OR) of 1.79 for having kidney stones compared with men with normal blood pressure. Several prospective studies also demonstrated the relationship between nephrolithiasis and hypertension. Borghi et al. [28], after an 8-year follow-up of 140 hypertensive and 140 normotensive patients, showed that hypertensive patients had a significantly increased incidence of stone episodes (OR 5.5). Several studies also revealed an increased risk of hypertension in those with nephrolithiasis [29]. This evidence suggests that the relationship is reciprocal, but the physiological pathways linking both diseases have not been well described. Animal studies have consistently shown hypercalciuria and metabolic acidosis in hypertensive rodent models [30]. The research of Eisner et al. [31] has confirmed that there is an increased excretion of calcium in hypertensive patients. Another possible mechanism may be the hypocitraturia, which occurs secondary to acidosis in hypertensive patients.

However, there are also studies that did not demonstrate this relationship. Madore et al. [32] conducted a prospective study to clarify the role of hypertension in kidney stone disease. They used data collected during the Health Professionals Follow-up Study (HPFS), a longitudinal study of cardiovascular disease and cancer in men. The initial results revealed an age-adjusted OR of 1.31 between hypertension and nephrolithiasis in a cross-sectional analysis. Follow-up data showed a greater tendency to develop hypertension in individuals with a history of urolithiasis. However, hypertensive patients did not have a higher incidence of new stones as had been shown in previous studies. The study confirmed the association between hypertension and nephrolithiasis, but the authors suggested that it was nephrolithiasis that increased the risk of hypertension. In our study, we found results similar to those from Cappucio et al. in which a significant correlation existed between hypertension and urinary stone disease with an OR of 3.

Our study has several inherent limitations. Because the study was performed via survey, we did not have the opportunity to obtain certain clinical data, such as stone composition or laboratory studies. Diabetes and urinary stone disease were self-reported so that reporting errors or the presence of silent diseases may have skewed our results. However, our interviewers (senior medical students) assessed the reported diseases and drug usage through the medical records of the participants. Only participants with definitive urolithiasis were included in the statistical analysis. However, some of the participants with possible urolithiasis or with the presence of undiagnosed silent stones may have actually had urinary stone disease. Our urinary stone disease ratio, then, may have been lower than the actual ratio. Finally, the association between the MS and the prevalence of kidney stones might be reduced if adjusted models for covariables such as salt intake, protein intake, and gender were used.

Conclusions

Patients who have metabolic syndrome components are at a higher risk for developing urolithiasis. The risk also increases with the number of components that patients have. Among the components, the risk for the development of urolithiasis is most significantly associated with the patient's BMI and the presence of hypertension.

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