

Epidemiologic study of urolithiasis in seven countries of South-Eastern Europe: S.E.G.U.R. 1 study

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Summary Objective: To investigate some epidemiological aspects of kidney stones in the South-Eastern European area.

Materials and methods: From September 2015 to December 2015, 538 consecutive patients were treated and evaluated for reno-ureteral stones in eight departments in Bulgaria, Greece, Italy, FYR Macedonia, Romania, Serbia and Turkey.

Results: The age of onset was lower in Turkey and higher in Italy. The rate of recurrent patients was higher in Romania and Serbia, while first renal stone formers were more frequent in Italy. The previous history of kidney stones, the characteristics of the stones and the dietary habits of the patients were different in different countries. In Bulgaria, Greece and Romania larger calculi from recurrent patients were more frequent. In Italy and Turkey smaller calculi from first renal stone formers were more frequent.

Conclusions: The previous history of kidney stones, the characteristics of the stones and the dietary habits of the patients were different in different countries. A common dietary pattern associated with the formation of kidney stones was not observed, but each country showed different risk factors.

KEY WORDS: Urolithiasis; Epidemiology; Diet.

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INTRODUCTION

The epidemiology of urolithiasis has been frequently correlated with geography, climate and culture (1).

The area of South Eastern Europe is relatively homogeneous in topography, climate and eating habits. In some countries of this area the prevalence of urolithiasis was assessed according to population-based studies. In Italy, the prevalence was estimated at 6.8% (males) and 4.9% (females) in 1986 and 10.1% (M) and 5.8% (F) in 1998 (2), in Turkey it amounted to 14.8% in 1989 (3) and in Greece 15% in 2006 (4). Limited information is available about renal stone prevalence in Bulgaria, FYR Macedonia,

Romania and Serbia (5). These prevalence rates are higher than those reported in other regions of Europe such as Germany (4.7%) (6) and the United Kingdom (3.5%) (7) and can be explained by the warmer climate. On the contrary, the South-East European area is characterized by the consumption of the Mediterranean diet, that has long been associated with lower incidence of cardiovascular disease and cancer (8, 9). Some components of the Mediterranean diet as vegetables, fruits, potatoes, legumes and dairy products may be potentially favorable for the prevention of kidney stones.

Aim of this study was to evaluate several epidemiological features and dietary habits, in patients with renal stones treated in seven countries of the South-Eastern Europe.

MATERIALS AND METHODS

From September 2015 to December 2015, 538 consecutive patients were treated for reno-ureteral stones in eight urological departments in Bulgaria, Greece, Italy, FYR Macedonia, Romania, Serbia and Turkey. The patients were evaluated on the basis of a questionnaire posted on www.segurgroup.eu website. The questionnaire investigated extensively patient characteristics, including age, gender, weight, height, body mass index (BMI), working and sporting activity, bowel habits, urinary volume, presence of urological diseases or medical diseases related to stone formation, previous urinary tract infection, renal function, fluid intake and dietary habits, stone history and stone characteristics (size, location, composition, side and treatment modality).

Working activity was scored as light, heavy and very heavy and sporting activity as light, intermediate, high and professional; intake of food categories (pasta/rice/pizza, meat/poultry/fish, cheese, vegetables, fruit) as never or rarely, often, daily; milk/yogurt intake as n° cups/day; bread intake n° of loafs/slices/day. Working activity and

dietary assessment was carried out by the Urologist which interviewed the patients by recall method.

The results of the questionnaire were compared according to the country of the evaluated subjects. Stone analysis was performed on the 360 out of 538 patients (the ESWL patients didn't have stone analysis) and was mainly chemical analysis (82%) whereas the rest by diffractometry.

Statistical analysis

Normality was tested using the *Shapiro-Wilk* test. Normally distributed data were presented as mean (S.D.) as for not normally distributed data median and *interquartile range* (IQR) were used. Comparisons between countries for normally distributed data was conducted using ANOVA. Comparisons for not normally distributed data was performed using *Kruskal-Wallis* test. *Fisher's* exact test was applied for comparisons with categorical data. *Dunn's* multiple comparisons test was applied after a significant *Kruskal-Wallis* or *Fisher's* exact test. *Sidak* correction was used for multiple comparisons between countries. Analysis was conducted using *StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP.*

RESULTS

A total of 538 patients were enrolled of whom 124 from *Bulgaria*, 17 from *FYR Macedonia*, 50 from *Greece*, 65 from *Italy*, 122 from *Romania*, 55 from *Serbia* and 106 from *Turkey*.

Gender and age

In total the male to female ratio (M/F) was 1.07 with a 0.82 in *Bulgaria*, 1.42 in *FYR Macedonia*, 1.77 in *Greece*, 1.5 in *Italy*, 1.03 in *Romania*, 0.62 in *Serbia* and 1.23 in *Turkey*. Difference of distribution of the disease by gender for different countries was not significant ($p = 0.065$).

Age at stone onset was 39.9 ± 16.2 in the total population with significant differences between different countries ($p < 0.001$). In *Turkey* it was significantly lower than in *Greece*, *Italy*, *Romania* and *Serbia* whereas in *Bulgaria* and *FYR Macedonia* it was significantly lower than in *Greece* and *Italy* (Table 1).

Height, weight and BMI

There were no statistically significant differences between patients from different countries for height, weight and BMI (Table 1).

There was a statistically significant difference by gender for weight ($p < 0.001$), height ($p < 0.001$) and BMI ($p < 0.001$). No statistical significant differences of weight (ANOVA F-test = 0.185) and BMI (ANOVA F-test = 0.185) were observed in women by different countries. Height of women by different countries was significantly different (ANOVA F-test < 0.001) with Serbian female patients taller than female patients of other countries (ANOVA F-test < 0.05) except patients from *FYR Macedonia*.

Statistical differences of height, weight and BMI (ANOVA F-test < 0.001) were observed in men from different countries.

Male Turkish patients were shorter than patients from all other countries but male patients from *Italy* (ANOVA F-test < 0.05).

Male Bulgarian patients were significantly heavier than male patients from *Italy*, *Turkey* and *Romania* (ANOVA F-test < 0.05) and showed higher BMI scores than male patients from *Serbia* and *Romania*. Also male patients from *Turkey* had higher BMI scores than patients from *Romania* (ANOVA F-test < 0.05).

Urological and medical diseases

Urological anomalies were observed in 63/538. The more common were urethral stenosis (5.39%), ureteral stenosis (2.6%), ureteropelvic junction (UPJ) stenosis (2.33%) and horseshoe kidney (1.49%).

Medical diseases related to renal stone formation were observed in 118/538. The more frequent were bone disease (6.51%), peptic ulcer (6.13%), gout (3.35%), hyperthyroidism (2.24%), diabetes mellitus (2.23%) hyperparathyroidism (1.35%).

Statistically significant different rates of urological diseases and of medical diseases related to stone formation were observed for patients from different countries (chi-2 test $p < 0.001$ and $p = 0.016$) with the highest rate of urological diseases observed in *Romania* (73.7%) and *FYR Macedonia* (88.2%) and the highest rate of medical diseases in *Turkey* (40%).

Working and sporting activity

Statistically significant difference was observed for working and sporting activity between patients from different countries ($p = 0.001$ and $p = 0.005$) (Table 1).

Bulgarians patients had heavy working activity (47.6%) with respect to patients from other countries (20-32.8%). Heavy or intermediate sporting activity was more frequent in patients from *Bulgaria* and *Serbia* (51.8% and 50%) with respect to other countries (14%-43.8%).

Dietary habit

Intakes of pasta, meat, cheese, vegetables, fruit, milk and bread were significantly different in different countries (ANOVA F-test < 0.001) (Table 2).

Patients from *Italy* tended to consume more pasta products (pasta/rice/pizza) in comparison with patients from all other countries ($p < 0.05$ in all comparisons) except patients from *FYR Macedonia*. Patients from *Romania* tended to consume less pasta products in comparison with patients from *Greece*, *FYR Macedonia* and *Turkey* ($p < 0.05$ in all comparisons) and patients from *Bulgaria* tended to consume less pasta in comparison with patients from all other countries ($p < 0.05$).

Patients from *Romania* tended to consume less vegetables in comparison with patients from all other countries ($p < 0.05$) and those from *Serbia* more vegetables than those from *Turkey* ($p < 0.05$).

Patients from *Italy* and *FYR Macedonia* tended to consume more fruits in comparison with patients from all other countries ($p < 0.05$).

Patients from *Romania* tended to consume more bread in comparison with patients from all other countries except patients from *FYR Macedonia* ($p < 0.05$) and patients

Table 1.
Demographic and clinical data of patients by different countries.

	Bulgaria (n = 124)	FYR Macedonia (n = 17)	Greece (n = 50)	Italy (n = 65)	Romania (n = 122)	Serbia (n = 55)	Turkey (n = 106)	Overall (n = 538)	P value
Gender†									0.065
Female	54.8%	41.2%	36.0%	40.0%	49.2%	61.8%	44.8%	48.3%	
Male	45.2%	58.8%	64.0%	60.0%	50.8%	38.2%	55.2%	51.7%	
BMI‡	27.4 (5.52)	25.1 (2.65)	26.9 (3.62)	26.0 (4.31)	26.7 (6.07)	26.7 (8.43)	26.5 (4.93)	26.7 (5.57)	0.022
Age‡	52.5 (13.67)	49.9 (15.93)	57.1 (13.70)	50.3 (15.23)	44.7 (15.23)	50.3 (13.35)	43.3(14.88)	48.8(15.10)	0.593
Age onset‡	37.1 (17.43)	36.1 (12.30)	47.3 (17.82)	44.9 (17.86)	42.5 (16.32)	42.4(10.86)	33.8(12.52)	39.9(16.18)	< 0.001
First time former	33.9% (n = 42)	35.3% (n = 6)	34.0% (n = 17)	56.9% (n = 37)	14.7% (n = 104)	1.8% (n = 1)	37.1% (n = 39)	45.7% (n = 246)	-
Recurrence£	0.16 [0.09-0.40]	0.17 [0.10-0.40]	0.37 [0.15-0.60]	0.20 [0.13-0.48]	1.0 [0.25-1.0]	0.71 [0.50-1.0]	0.29 [0.14-0.60]	0.37 [0.14-0.84]	< 0.001
Working activity†									0.001
Light	52.4%	76.5%	72.0%	67.2%	75.2%	80.0%	72.6%	68.7%	
Heavy	47.6%	23.5%	28.0%	32.8%	24.8%	20.0%	27.4%	31.3%	
Sports†									0.005
Light	48.2%	75.0%	86.0%	58.1%	55.7%	50.0%	66.1%	62.1%	
Intermediate	48.2%	25.0%	12.0%	32.3%	39.3%	39.3%	23.7%	31.9%	
Heavy	3.6%	0.0%	2%	9.7%	4.9%	10.7%	10.2%	6.0%	
Bowel†									0.002
Regular	79.0%	52.9%	82.0%	79.0%	69.2%	78.4%	58.0%	72.1%	
Non - regular	21.0%	47.1%	18.0%	21.0%	30.8%	21.6%	42.0%	27.9%	
Renal insufficiency†									< 0.001
< 1.2	79.0%	70.6%	84.0%	76.7%	52.7%	74.6%	89.6%	74.7%	
> = 1.2	21.0%	29.4%	16.0%	23.3%	47.3%	25.4%	10.4%	25.3%	

† Fisher's exact test.
‡ Data presented as Mean (S.D.). One-way ANOVA conducted for comparisons between nations.
£ Data presented as Median [IQR]. Dunn test (median test) conducted for multiple comparisons.
*IQR = Interquartile Range.

Table 2.
Dietary patterns of patients by different countries.

	Bulgaria	FYR Macedonia	Greece	Italy	Romania	Serbia	Turkey	Overall	P value
Pasta/rice/pizza/etc.†									< 0.001
Never/rarely	81.5%	23.5%	8.0%	8.1%	52.5%	25.4%	30.4%	41.9%	
Often	17.7%	17.7%	68.0%	17.7%	43.4%	58.2%	24.5%	33.8%	
Daily	0.8%	58.8%	24.0%	74.2%	4.1%	16.4%	45.1%	24.3%	
Meat (any type)†									< 0.001
Never/rarely	13.7%	29.4%	6.0%	3.2%	3.3%	0.0%	19.6%	9.6%	
Often	56.5%	23.5%	72.0%	24.2%	82.6%	80.0%	56.9%	61.6%	
Daily	29.8%	47.1%	22.0%	72.6%	14.1%	20.0%	23.5%	28.8%	
Cheese†									< 0.001
Never/rarely	11.3%	11.8%	6.1%	29.0%	4.1%	50.9%	18.6%	16.8%	
Often	55.6%	23.5%	53.1%	35.5%	87.6%	47.3%	34.3%	54.3%	
Daily	33.1%	64.7%	40.8%	35.5%	8.3%	1.8%	47.1%	28.9%	
Vegetables†									< 0.001
Never/rarely	1.6%	0.0%	10.0%	21.0%	0.8%	0.0%	12.0%	6.3%	
Often	44.7%	11.8%	36.0%	19.3%	81.7%	23.6%	32.0%	43.6%	
Daily	53.7%	88.2%	54.0%	59.7%	17.5%	76.4%	56.0%	50.1%	
Fruits†									< 0.001
Never/rarely	19.4%	5.9%	36.0%	19.4%	16.5%	9.1%	29.4%	20.7%	
Often	55.6%	23.5%	30.0%	3.2%	68.6%	81.8%	34.3%	47.7%	
Daily	25.0%	70.6%	34.0%	77.4%	14.9%	9.1%	36.3%	31.6%	
Milk†									< 0.001
Never	9.7%	0.0%	68.0%	41.0%	29.7%	0.0%	19.6%	24.0%	
1-2/day	80.6%	87.5%	30.0%	59.0%	64.4%	63.0%	51.0%	62.3%	
3 or more/day	9.7%	12.5%	2.0%	0.0%	5.9%	37.0%	29.4%	13.7%	
Bread†									< 0.001
Never	4.0%	0.0%	6.0%	16.1%	0.0%	0.0%	6.9%	4.7%	
1-2/day	42.8%	58.8%	50.0%	79.0%	25.4%	63.0%	47.0%	47.1%	
3 or more/day	53.2%	41.2%	44.0%	4.9%	74.6%	37.0%	46.1%	48.2%	

† Fisher's exact test.
Comment: Dunn's test implemented for multiple comparisons of eating habits between patients from different nations.

from Italy less bread in comparison with patients from all other countries ($p < 0.05$).

Patients from *Serbia* tended to consume more milk than patients from all other countries except *FYR Macedonia* and *Turkey* ($p < 0.05$) and patients from *Bulgaria* and *Turkey* tended to consume more milk in comparison with patients from *Greece*, *Italy* and *Romania* ($p < 0.05$). Patients from *Italy* tended to consume more meat products in comparison with patients from all other countries ($p < 0.05$ in all comparison). Patients from *Serbia* tended to consume more cheese product in comparison with patients from all other countries ($p < 0.05$ in all comparisons) and patients from *FYR Macedonia* to consume more cheese products than those from *Romania* ($p < 0.05$).

DISCUSSION

Several studies have shown that urinary calculi tend to be more frequent in men, although infection stones were often more frequently reported in women (10,11). Our study confirmed that nephrolithiasis is more frequent in men, although in *Bulgaria* and *Serbia* we observed more stones in women.

This can be explained by the higher rate of infection stones in Bulgarian patients with respect to patients from other countries. The rate of infection stones in *FYR Macedonia* was much higher but the number of patients from this country was very low. On the other hand, stones were more frequent in females also in *Serbia*, but information of stone composition from this country was limited.

Age at stone onset was lower in *Turkey* and *Bulgaria* and higher in *Italy*.

Stone onset of hereditary stones, such as cystine, tend to be low whereas uric acid stone formation is typical of older patients. In our series, cystine stones were more frequent in *FYR Macedonia* and, at a lesser extent, in *Turkey* and *Bulgaria* and uric acid stones were less frequent in *FYR Macedonia* and *Turkey* than in other countries.

A higher rate of hereditary stones together with a lower rate of uric acid stones could be an explanation of the lower age at stone onset in *Turkey*. In *Italy* the higher age at stone onset could be related to the prevalence of first renal stone formers that are characterized by a later onset of stone disease (12).

The dietary pattern correlated with renal stone formation is complex, because the risk of renal calcium stone formation may depend on a reduced intake of fluids, an insufficient calcium intake, an increased intake of protein and sodium and a reduced intake of potassium (13). Consequently, the formation of calcium stones can be favored by reduced fluid intake, excessive consumption of meat, a low intake of milk and dairy products and insufficient consumption of vegetables. Not necessarily all of these factors must coexist simultaneously, as it is the sum of the effects of each of them to determine the risk of kidney stones (14).

For this reason, it is not surprising to observe different dietary patterns in patients living in different countries where the diet may be different due to geographical, cultural and socioeconomic factors.

Our study was not specifically designed to evaluate stone

prevalence in different countries or the potential role of diet in renal stone formation because of the absence of control subjects, but it interestingly demonstrated that renal stone patients from different countries show different dietary patterns.

In *Italy*, socioeconomic changes of the past 50 years have resulted in a progressive abandonment of the traditional Mediterranean diet.

Today, the daily consumption of pasta and rice remained frequent, but the daily meat consumption increased (1 or more servings per day in 75% of cases), while the consumption of cheese and milk is relatively infrequent (never or rarely in 29 and 41%).

The dietary pattern of stone patients in *Bulgaria*, *Greece* and *Turkey* tends to be similar with a moderate consumption of meat (1 or more servings a day only in 29.8%, 22% and 23.5%) and a decent cheese consumption (never or rarely in 11.3%, 6.1% and 18.6%). However, the consumption of vegetables and fruit in these countries is relatively low (1 or more servings of vegetables and fruit per day of 53.7 + 25%, 54 + 34% and 56 + 36.3%, respectively) and milk consumption in *Greece* is low (never or rarely in the 68%).

In *Romania* and *Serbia*, the consumption of meat and cheese is high (often in 82.6% + 87.6% and 80% + 47.3%), but the consumption of vegetables and fruits is very low in *Romania* (1 or more servings a day in 17.5 and 14.9%) and that of fruit is low in *Serbia* (1 or more servings per day in 9.1%); also the consumption of milk is reduced in *Romania* (never in 29.7%).

CONCLUSIONS

In conclusion different dietary patterns can be observed in renal stone formers by different countries: high meat/low dairy in *Italy*, moderate meat & cheese/low fruit & vegetables in *Greece*, *Bulgaria* and *Turkey*, high meat/low vegetables (or fruit) in *Romania* and *Serbia*.

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