

Does smoking have any effect on urinary stone composition and the distribution of trace elements in urine and stones?

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Abstract The role of particular elements in lithogenesis is still unclear and debated. Probably some of them may promote or conversely inhibit crystal nucleation of organic or mineral species. A few epidemiological data link smoking with the risk of calcium stones. The aim of this hospital-based study was to evaluate the distribution of trace elements in urine and urinary stones, and possible correlation with stone constituents in smoking and non-smoking individuals. 209 stones and urine samples collected from idiopathic stone-formers were analyzed to evaluate the mineral composition and the distribution of elements, 29 in stones and 21 in urine. Values were statistically compared considering smoking, arterial hypertension and coronary heart disease as grouping variables. No differences were

noted either for comparison of mineral components or the elements concentrations in stones in both groups. The concentration of mercury in urine was higher in smokers than in non-smokers, but the statistical significance was at the moderate level. Our findings do not support the concept of possible association between smoking and urinary lithogenesis, but we believe that further investigations are needed in this area.

Keywords Urolithiasis · Urine · Trace elements · Smoking

Introduction

Urinary stones disease and its complications affect 5–15% of population in industrialized countries [1]. The rising prevalence and high recurrence rate induce to consider urolithiasis as serious socio-medical problem. Although important advances have been made in understanding the multifactorial pathophysiology of stone formation, none of many theories has given a complex and satisfactory explanation of this process. The crystallization of supersaturated urine components is modified by the activity of promoters and inhibitors, and some morphoanatomic, dietary, and environmental factors [2, 3]. It has been underlined by many authors that formation of calcium oxalate stones in urinary tract may be associated with different pathologies from alimentary disorders to genetic pathology [4, 5]. The role of trace elements in lithogenesis is not yet known and still debated [6–8]. Some of them affect crystallization of stone components by means of acting at the surface of the crystals since their concentration in urine is too small to affect the lattice ions in solution [9, 10]. It has been demonstrated by some authors that such metals as magnesium,

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zinc, aluminum, iron and copper may act as inhibitors of calcium oxalate growth at very low concentrations [7, 10]. Probably some other elements may also promote or conversely inhibit the crystal nucleation of organic or mineral species involved in lithogenesis, but the reports are often conflicting. The concentration of heavy metals in body tissues is elevated in cigarette smokers having an important influence of several diseases such as cancers [11, 12]. Some epidemiological data link smoking with the risk of calcium stones [13]. The aim of this hospital-based study was to evaluate a distribution of trace elements in urine and urinary stones and possible correlation with stone constituents in smoking and non-smoking individuals.

Materials and methods

The project was approved by Ethic Committee of Pomeranian Medical University in Szczecin, Poland. All patients gave written informed consent for the participation in this study. 219 stones were obtained from consecutive patients admitted to the Department of Urology between June 2007 and March 2009. The study protocol did not include the patients in whom the non-idiopathic but obstructive origin of urolithiasis was suspected based on intravenous pyelography and/or computed tomography. The mean age of patients was 55.4 years and the group comprised 121 females and 98 males. Most of the stones ($n = 153$, 69.9%) were collected after percutaneous nephrolithotripsy procedure, 50 (22.8%) after ureteroscopic lithotripsy, 4 (1.8%) after extracorporeal shockwave treatment, and 12 (5.5%) were removed from specimens after nephrectomy performed because of end-stage hydro- or pyonephrosis. All patients were asked to fill the questionnaire which included questions about their health problems, the family and stone disease history, smoking and dietary habits. The urine was collected from all patients during their hospital stay from 24-h urine sample. Each urine sample was frozen in temperature -80°C and defrozen just before analysis. Each stone was weighed, divided into two parts, and crushed before analysis. One part was assayed with wet chemical methods [14, 15]. They do not provide data regarding the crystalline structure, but make possible sensitive and precise quantitative stone composition analysis. The mineral content (calcium and magnesium) was evaluated using atomic absorption spectrometry (Philips PU 9100X, Germany) and organic compounds (uric acid, xantine, cystine) with spectrophotometry (Lambda 40P, Perkin Elmer, USA). The distribution of phosphorus was measured using colorimetric method (Analco Medical Trade, Poland). Most of the stones were of mixed structure with one leading component; therefore, the mineral composition was evaluated as percents of total weight. Because of the low rate of

struvite and brushite stones and their comparable chemical composition, they were merged into one group of magnesium phosphate. Additionally, phosphate salts (calcium + magnesium) and calcium salts (oxalates + phosphates) were evaluated. The other part of the stones was combusted in microwave mineralizer ETHOS (Milestone, USA). The concentrations of 28 elements Ca, Na, K, P, Zn, Mg, Fe, Cu, Sr, Ni, Mn, Se, Cr, Mo, Co, Li, V, Al, Pb, Cd, B, Ba, Hg, Ge, Si, I, As, and Sn were determined. Multi-elemental analysis was performed with inductively coupled plasma-atomic emission spectrometry (ICP-OES Optima 5300DV, Perkin Elmer, USA). Using the same method the level of 21 elements was determined in urine: Ca, Na, K, P, Zn, Mg, Fe, Cu, Sr, Ni, Mn, Cr, Mo, Co, Li, V, Al, Pb, Cd, B, and Hg.

Element concentrations were described in terms of mean, standard deviation (SD), median, and interquartile range (IQR). The normality of the data was checked with Shapiro–Wilk's test. Values were statistically compared using Mann–Whitney test considering smoking, arterial hypertension, and coronary heart disease as grouping variables. Statistical significance was determined as $p < 0.05$. Statistica 7.1 software was used for calculation.

Results

The mean age of the first episode of kidney stone disease was 45.3 ± 16.1 , and 143 patients (65.3%) had already at least one episode of recurrence. 40.2% of group ($n = 88$) had positive family history of urolithiasis. There were 156 non-smoking and 63 smoking patients in the studied group. The mean weight of the stone sent to analysis was 165.5 mg (minimum 3, maximum 3,815 mg). The mean volume of 24-h urine sample was $1,669 \pm 336$ ml. The most common components of all analyzed stones were calcium oxalate ($58.6 \pm 37.62\%$) and calcium phosphates ($25.33 \pm 27.99\%$). Uric acid ($11.76 \pm 29.95\%$) and magnesium phosphate ($4.28 \pm 12.19\%$) were found in lower amounts. The mean concentrations of elements in stones and urine along with relevant standard deviation and median with interquartile range are presented in Tables 1 and 2. The elements in tables are listed according to their position in periodic table.

Concentration of Li, Na, K, Mg, Ca, Sr, Ba, Cr, Mg, V, Ni, Cu, Zn, Cd, Hg, Al, Ge, Sn, Pb, P, and I in urinary stones was higher in group of smokers. The levels of Mn, Fe, Co, B, Si, As, and Se were lower in this group, but no statistical significance was noted either in comparing the mineral components or the elements concentrations in stones in the both groups (Tables 3, 4). However, higher concentrations of Zn and Sr in smokers' stones were close to the significance ($p < 0.06$). The concentration of only one element (Hg) in urine was higher in smokers than in

Table 1 The studied element levels in stones ($n = 219$)

Element ($\mu\text{g/g}$)	Mean \pm SD	Median (IQR)
Li	0.128 \pm 0.263	0.041 (0.075)
Na	592.42 \pm 218.21	576.90 (189.21)
K	408.44 \pm 172.42	380.17 (250.74)
Mg	528.11 \pm 983.62	170.1 (479.97)
Ca	34,490 \pm 20,882	33,187 (27139)
Sr	14.46 \pm 13.85	10.8 (16.4)
Ba	1.74 \pm 2.46	1 (1.4)
Cr	1.15 \pm 1.75	0.56 (1.24)
Mo	0.0203 \pm 0.0265	0.012 (0.027)
V	0.238 \pm 0.629	0.022 (0.074)
Mn	2.39 \pm 2.86	1.35 (1.66)
Fe	19.75 \pm 44.20	2.904 (15.2)
Co	0.216 \pm 0.497	0.054 (0.137)
Ni	2.05 \pm 2.52	1.59 (1.54)
Cu	3.79 \pm 4.23	2.9 (3.026)
Zn	187.23 \pm 184.78	144.37 (221.46)
Cd	0.155 \pm 0.279	0.0625 (0.09)
Hg	0.0295 \pm 0.0794	0.0128 (0.0399)
B	8.47 \pm 19.43	1.34 (5.77)
Al	7.18 \pm 13.19	3.57 (7.62)
Si	8.46 \pm 23.23	2.4 (9.4)
Ge	0.104 \pm 0.141	0.056 (0.0648)
Sn	0.156 \pm 0.344	0.007 (0.149)
Pb	4.32 \pm 7.16	1.39 (5.12)
P	12,047 \pm 13,198	6,348.3 (16688)
As	0.159 \pm 0.217	0.074 (0.169)
Se	3.16 \pm 3.82	1.76 (3.38)
I	4.14 \pm 6.07	1.9 (4.6)

non-smokers, but the statistical significance was at the moderate level ($p = 0.045$) (Table 5). Similar to stones, little higher Sr concentration was observed in smokers ($p < 0.07$).

Discussion

Although the initial papers on trace elements in urinary stones were published in the 1950s, so far little data has been presented that would link the presence or absence of certain trace elements in the urine of stone formers to the pathogenesis of this disease [7, 16, 17]. The results of many studies suggest that some elements including Ni, Mg, Cr, Al, Pb, Cd, and Cu together with other factors may affect the process of stone precipitation [18, 19]. On the other hand, most theories explaining the pathogenesis of stones formation do not include any role of trace elements. A special attention is generally paid to different socioeconomic, alimentary, occupational, and environmental factors.

Table 2 The studied element levels in urine ($n = 219$)

Element ($\mu\text{g/ml}$)	Mean \pm SD	Median (IQR)
Li	0.0155 \pm 0.0196	0.0112 (0.0156)
Na	4,078.85 \pm 1,510.8	3,971.1 (2.155)
K	1,939.11 \pm 861.67	1,856.62 (1,101.94)
Mg	209.01 \pm 77.92	193.73 (84.59)
Ca	117.34 \pm 56.84	103.41 (75.19)
Sr	0.0896 \pm 0.983	0.06 (0.108)
Cr	0.0235 \pm 0.0129	0.0217 (0.0113)
Mo	0.0108 \pm 0.0102	0.00705 (0.0969)
V	0.00518 \pm 0.0785	0.01 (0.00865)
Mn	0.0146 \pm 0.0132	0.012 (0.0126)
Fe	0.0315 \pm 0.0362	0.016 (0.0261)
Co	0.00507 \pm 0.0678	0.0026 (0.00453)
Ni	0.0722 \pm 0.134	0.0362 (0.0541)
Cu	0.0109 \pm 0.00961	0.00786 (0.0675)
Zn	0.281 \pm 0.205	0.235 (0.225)
Cd	0.00263 \pm 0.00436	0.00125 (0.0006)
Hg	0.000229 \pm 0.00111	0 (0)
B	0.255 \pm 0.284	0.154 (0.226)
Al	0.178 \pm 0.105	0.158 (0.115)
Pb	0.0144 \pm 0.0233	0.00933 (0.0134)
P	464.53 \pm 321.18	369.21 (273.3)

Only few papers report the influence of smoking on lithogenesis. Liu et al. [13] evaluated the impact of cigarette smoking and betel quid chewing on the risk of calcium urolithiasis treating them as independent risk factors. The risk increased 3.73-fold (OR 3.73, 95%CI, 1.81–7.70, $p < 0.001$) when both habits were joined. Hamano et al. [20] confirmed that calcium oxalate stones are strongly associated with several coronary heart disease risk factors including smoking habits and hypertension. We observed no differences in element levels in stones comparing patients with ($n = 88$) and without arterial hypertension ($n = 131$) and with ($n = 16$) and without diagnosis of coronary heart disease ($n = 203$) (data not shown). One of the possible factors which may explain this effect is high body Cd and Pb level because of heavy smoking [21–23]. Urinary tract stones were found to be more common among workers, chronically exposed to Cd as compared to general population [24, 25]. In our study, we did not find any difference between Cd and Pb levels in either groups. Higher mercury level in body tissues and biological materials e.g., hair and urine is usually found in workers exposed to mercury vapor or because of the presence of dental fillings containing this metal and therefore, we consider our result rather incidental. Zn and Sr content in stones of smokers were higher with borderline significance. This phenomenon may be associated with similarity between the ion charge and size of Zn and Sr and Ca which facilitates their

Table 3 Mineral composition of stones in non-smoking and smoking individuals

Mineral constituent (%)	Non-smokers (<i>n</i> = 156)		Smokers (<i>n</i> = 63)		<i>p</i>
	Mean \pm SD	Median (IQR)	Mean \pm SD	Median (IQR)	
Calcium oxalates	58.33 \pm 38.23	73.75 (80)	59.29 \pm 36.36	70 (65)	0.96
Calcium phosphates	23.99 \pm 27.74	11.5 (42)	28.65 \pm 28.56	17 (47)	0.17
Uric acid	13.74 \pm 32.29	0 (0)	6.87 \pm 22.66	0 (0)	0.17
Magnesium phosphate	3.92 \pm 11.33	0 (0)	5.19 \pm 14.16	0 (2)	0.41
Phosphate salts	27.9 \pm 34.4	11.5 (42)	33.84 \pm 35.67	17 (52)	0.15
Calcium salts	82.31 \pm 32.61	100 (20)	87.94 \pm 25.42	100 (4)	0.43

Table 4 The distribution of studied elements in stones of non-smoking and smoking individuals

Element ($\mu\text{g/g}$)	Non-smokers (<i>n</i> = 156)		Smokers (<i>n</i> = 63)		<i>p</i>
	Mean \pm SD	Median (IQR)	Mean \pm SD	Median (IQR)	
Li	0.113 \pm 0.192	0.0463 (0.0845)	0.163 \pm 0.386	0.034 (0.07)	0.33
Na	582.41 \pm 215.58	576.94 (186.85)	617.20 \pm 224.42	576.90 (213)	0.34
K	407.77 \pm 173.51	382.10 (254.86)	410.10 \pm 171.06	370.10 (241.09)	0.85
Mg	487.03 \pm 894.45	144.6 (465.27)	629.84 \pm 1177	241.5 (454.2)	0.072
Ca	33,473 \pm 21,539	31,585 (26,972)	37,009 \pm 19,091	35,784 (24,161)	0.17
Sr	13.44 \pm 13.44	9.5 (16.54)	16.99 \pm 14.63	14.4 (18.85)	0.053
Ba	1.62 \pm 2.15	0.91 (1.295)	2.05 \pm 3.08	1.203 (1.99)	0.43
Cr	1.069 \pm 1.51	0.581 (1.29)	1.35 \pm 2.22	0.504 (1)	0.96
Mo	0.0183 \pm 0.02203	0.011 (0.0237)	0.0255 \pm 0.0349	0.016 (0.0299)	0.17
V	0.2101 \pm 0.508	0.022 (0.0749)	0.307 \pm 0.861	0.02 (0.0549)	0.77
Mn	2.49 \pm 2.97	1.4 (1.89)	2.16 \pm 2.59	1.21 (0.742)	0.31
Fe	22.2 \pm 48.9	3.5 (16.05)	13.67 \pm 28.96	2.2 (11.8)	0.59
Co	0.238 \pm 0.545	0.0558 (0.154)	0.161 \pm 0.348	0.0463 (0.0773)	0.063
Ni	2.049 \pm 2.74	1.59 (1.56)	2.062 \pm 1.89	1.6 (1.45)	0.63
Cu	3.64 \pm 3.67	3.086 (2.69)	4.17 \pm 5.41	2.8 (3.3)	0.9
Zn	173.16 \pm 180.54	123.5 (210.74)	222.06 \pm 191.91	177.61 (230)	0.054
Cd	0.148 \pm 0.221	0.07 (0.103)	0.171 \pm 0.387	0.0529 (0.0699)	0.63
Hg	0.0247 \pm 0.0271	0.0127 (0.0399)	0.0415 \pm 0.142	0.0128 (0.0259)	0.87
B	9.04 \pm 20.11	1.49 (6.85)	7.05 \pm 17.72	0.80 (2.67)	0.19
Al	6.56 \pm 10.5	3.34 (7.36)	8.701 \pm 18.24	4.603 (8.29)	0.27
Si	9.54 \pm 26.60	2.55 (10.26)	5.77 \pm 10.9	1.29 (7.1)	0.086
Ge	0.1001 \pm 0.126	0.0555 (0.0655)	0.113 \pm 0.172	0.0576 (0.0603)	0.86
Sn	0.154 \pm 0.311	0.0085 (0.179)	0.162 \pm 0.417	0.00493 (0.0721)	0.5
Pb	4.23 \pm 6.85	1.36 (4.702)	4.56 \pm 7.92	1.49 (5.48)	0.98
P	11,692 \pm 13571	5,919.7 (16173)	12,925 \pm 12285	8,471.5 (17,355)	0.21
As	0.1701 \pm 0.218	0.0895 (0.209)	0.131 \pm 0.214	0.0548 (0.089)	0.18
Se	3.28 \pm 3.97	1.78 (3.62)	2.86 \pm 3.43	1.47 (2.77)	0.45
I	3.57 \pm 4.89	1.6 (4.12)	5.54 \pm 8.19	2.21 (5.15)	0.11

incorporation into calcium-containing stones. The data concerning the role of Zn and Sr in lithogenesis are divergent. Early studies by Bird and Thomas [26] and recent publications by Atakan et al. [6] showed that Zn's low level in the urine of stone formers suggests its potential inhibiting action. Other data, however, show increased excretion of Zn and Cu in stone formers or even no difference between stone formers and the healthy population [2, 8, 27]. Bazin

et al. [7], after an analysis of the distribution of seven metals in 78 stones, showed a high proportion of Zn and Sr in phosphate stone and contrary to Joost et al.'s results [8], a lower proportion of these elements in calcium oxalate stones.

The group from Finland studied the associations between a diet and the risk of kidney stones in a cohort of 27,001 male smokers aged 50–69 years who were initially

Table 5 The distribution of studied elements in urine of non-smoking and smoking individuals

Element ($\mu\text{g/ml}$)	Non-smokers ($n = 156$)		Smokers ($n = 63$)		p
	Mean \pm SD	Median (IQR)	Mean \pm SD	Median (IQR)	
Li	0.0151 \pm 0.0174	0.0111 (0.016)	0.0164 \pm 0.0242	0.012 (0.0158)	0.76
Na	4,084.65 \pm 1,544.49	3,974.7 (2,147.4)	4,064.47 \pm 1,435.86	3,964.588 (2,182.68)	0.88
K	1,898.77 \pm 806.63	1,850.22 (1,035.65)	2,038.97 \pm 984.78	1,896.96 (1,489.96)	0.47
Mg	205.75 \pm 72.79	193.46 (81.23)	217.09 \pm 89.47	195.73 (93.29)	0.63
Ca	117.8 \pm 58.03	103.39 (72.5)	115.9 \pm 54.23	103.89 (79.29)	0.8
Sr	0.084 \pm 0.099	0.049 (0.0944)	0.105 \pm 0.0964	0.0827 (0.137)	0.063
Cr	0.024 \pm 0.0147	0.0234 (0.0113)	0.0226 \pm 0.0069	0.02 (0.0115)	0.81
Mo	0.0104 \pm 0.0093	0.00711 (0.00924)	0.0119 \pm 0.0121	0.007 (0.00993)	0.97
V	0.00484 \pm 0.00718	0.001 (0.008)	0.006009 \pm 0.00929	0.00118 (0.0106)	0.66
Mn	0.0147 \pm 0.0143	0.0118 (0.01208)	0.0143 \pm 0.01001	0.0122 (0.0125)	0.44
Fe	0.0312 \pm 0.0342	0.0167 (0.0345)	0.0319 \pm 0.0413	0.0154 (0.0219)	0.77
Co	0.00486 \pm 0.00713	0.0025 (0.004301)	0.005601 \pm 0.00583	0.00283 (0.00603)	0.31
Ni	0.0751 \pm 0.137	0.039 (0.055)	0.0653 \pm 0.129	0.0322 (0.0446)	0.17
Cu	0.01069 \pm 0.00991	0.00754 (0.00622)	0.0113 \pm 0.00891	0.00897 (0.00771)	0.27
Zn	0.287 \pm 0.214	0.239 (0.223)	0.267 \pm 0.184	0.2 (0.24)	0.54
Cd	0.00243 \pm 0.00413	0.00127 (0.000515)	0.003102 \pm 0.00489	0.0012 (0.000634)	0.88
Hg	0.000197 \pm 0.00114	0 (0)	0.000307 \pm 0.00105	0 (0)	0.045*
B	0.253 \pm 0.283	0.157 (0.221)	0.258 \pm 0.286	0.148 (0.243)	0.93
Al	0.179 \pm 0.111	0.152 (0.127)	0.176 \pm 0.0882	0.172 (0.0854)	0.69
Pb	0.0134 \pm 0.02076	0.00913 (0.0132)	0.0169 \pm 0.0287	0.01 (0.0138)	0.39
P	445.76 \pm 220.54	368.26 (260.08)	511 \pm 487.88	373.44 (304.92)	0.8

* $p < 0.05$

free of kidney stones [28]. After 5 years of follow-up they found only 329 who had been diagnosed with kidney stones. Therefore, they concluded that smoking has not been found to be related to higher risk of lithogenesis. Although the data collected in our study do not support the concept of possible association between smoking, trace elements and urinary tract stones, we believe that further investigations are needed in this area.

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