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Can We Predict Urinary Stone Composition Based on an Analysis of Microelement Concentration in the Hair and Urine?*

Czy można przewidzieć skład kamieni moczowych na podstawie analizy zawartości mikroelementów we włosach i w moczu?

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Abstract

Background. In recent years the role of trace elements in lithogenesis has received steadily increasing attention.

Objectives. This study was aimed to attempt to find the correlations between the chemical content of the stones and the concentration of chosen elements in the urine and hair of stone formers.

Material and Methods. The proposal for the study was approved by the local ethics committee. Specimens were taken from 219 consecutive stone-formers. The content of the stone was evaluated using atomic absorption spectrometry, spectrophotometry, and colorimetric methods. An analysis of 29 elements in hair and 21 elements in urine was performed using inductively coupled plasma-atomic emission spectrometry.

Results. Only a few correlations between the composition of stones and the distribution of elements in urine and in hair were found. All were considered incidental.

Conclusions. The data obtained did not allow for the creation of a proper and practical algorithm to predict stone chemical composition based on hair and urine analysis (*Adv Clin Exp Med* 2012, 21, 4, 469–475).

Key words: urinary stone, urine, hair, analysis, trace elements.

Streszczenie

Wprowadzenie. W ostatnich latach obserwuje się rosnące naukowe zainteresowanie rolą mikroelementów w procesie tworzenia kamieni moczowych.

Cel pracy. Niniejsze badanie zostało podjęte w celu oceny potencjalnej korelacji między składem chemicznym kamieni a zawartością wybranych pierwiastków w moczu i we włosach chorych na kamicę dróg moczowych.

Materiał i metody. Projekt badania został zaakceptowany przez lokalny komitet etyczny. Próbkę pobierano od kolejnych 219 chorych na kamicę, kwalifikowanych do leczenia zabiegowego. Skład kamieni badano z zastosowaniem metod spektrometrii absorpcji atomowej, spektrofotometrii i kolorymetrii. Analiza zawartości 29 pierwiastków we włosach i 21 w moczu została wykonana z użyciem spektrometru emisji atomowej z plazmą wzbudzoną indukcyjnie.

Wyniki. Wśród badanych zależności stwierdzono jedynie pojedyncze, uznane za incydentalne, korelacje między składem kamieni a zawartością pierwiastków w badanych materiałach biologicznych.

Wnioski. Uzyskane dane nie pozwalają na stworzenie odpowiedniego, praktycznego algorytmu, na podstawie którego można byłoby przewidzieć lub odtworzyć skład chemiczny kamieni moczowych (*Adv Clin Exp Med* 2012, 21, 4, 469–475).

Słowa kluczowe: kamienie moczowe, mocz, włosy, analiza, pierwiastki śladowe.

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Urinary stones affect 2–20% of the population in industrialized countries, their prevalence is rising and they are considered a serious socio-medical problem [1–3]. Although important advances have been made in understanding the multifactorial pathophysiology of stone formation, there is not yet a complex and satisfactory explanation for this process. The process of crystallization of supersaturated urine components and the formation of solid concretions can be modified by the activity of promoters and inhibitors, and by some morpho-anatomic, dietary, and environmental factors. The role of trace elements in lithogenesis is still unclear and under debate. Some trace elements have an effect on the crystallization of stone components; they act at the surface of the crystals, as their concentration in urine is too small to affect the lattice ions in solution [4, 5]. It has also been documented that some trace elements influence the external morphology of growing crystals, and may increase or decrease the speed of the crystallization process [6, 7]. Some heavy metal ions, e.g. zinc and strontium, can substitute for calcium in crystals due to the similarity between the ions' charge and size. It has been demonstrated that metals such as magnesium, zinc, aluminum, iron and copper may act as inhibitors of calcium oxalate growth at very low concentrations [4, 8, 9]. It is probable that some other elements also promote or, conversely, inhibit crystal nucleation of the organic or mineral species involved in lithogenesis, but the reports are often conflicting. Some studies focus on determining the total levels of elements in studied materials; others focus on the elements' interactions with promoters or inhibitors such as citrate, glycosaminoglycans, pyrophosphate, and Tamm-Horsfall protein [6, 7, 10–14]. Many researchers have found correlations between essential elements in hair and metabolic disorders, diseases, nutritional status, and environmental exposures [15, 16]. Using hair to assess trace elements is controversial, but it has advantages over using blood or urine. Blood and urine represent current or recent body status, whereas hair is a reliable and convenient biological indicator reflecting long-term exposure [17, 18].

The query included in the title of this paper may seem to be weird. In a fact, if the answer is positive, we would have a practical tool for patients who, for instance, expelled their stones so it was lost for biochemical analysis.

Material and Methods

The proposal for the study was approved by the local ethics committee (No. BN-001/14/07, 28 Feb. 2007). All patients signed informed consent

forms for participation in this study. The stones were obtained from 219 consecutive patients admitted to the Department of Urology and Oncological Urology between June 2007 and March 2009 for upper urinary tract urolithiasis. The authors excluded the patients for whom, based on intravenous pyelography and/or computed tomography, the non-idiopathic but obstructive origin of urolithiasis was suspected. The authors also excluded individuals whose hair could include external contamination from hair dyes, local treatment agents (e.g. antifungal medication) or coloring shampoos. The mean age of patients was 55.4 years, and the group was comprised of 121 females and 98 males. Most of stones ($n = 153$, 69.9%) were collected after a percutaneous nephrolithotripsy (PCNL) procedure. In addition, 50 (22.8%) were collected after ureterorenoscopic lithotripsy (URL), four (1.8%) after extracorporeal shockwave treatment (ESWL), and 12 (5.5%) from specimens after a nephrectomy was performed in response to end-stage pyo- or hydronephrosis. Urine was collected from all patients during their hospital stay from a 24-h urine sample. Each sample was frozen at a temperature of -80°C and defrozen just before analysis. Each stone was weighed, divided into two parts, and crushed before analysis. The contents of the stone were evaluated using atomic absorption spectrometry (Philips PU 9100X, Germany) for calcium and magnesium, and spectrophotometry (Lambda 40P, Perkin Elmer, Massachusetts, USA) for organic compounds (uric acid, xanthine, 2,8-dihydroxyadenine, cystine). The distribution of phosphorus was measured using the colorimetric method (Analco Medical Trade, Warsaw, Poland). Most stones were of a 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, these stones were merged into one group of magnesium phosphate. Additionally, phosphate salts (calcium + magnesium) and calcium salts (oxalates + phosphates) were evaluated as individual groups. A total of 300–400 mg of hair was taken from the occipital region of the head, close to the scalp, and stored in labeled bags. The samples were washed in non-ionic detergents and dried. The stones and hair were combusted in an ETHOS 900 microwave mineralizer (Milestone, Connecticut, USA), and the concentrations of 29 elements, calcium (Ca), sodium (Na), potassium (K), phosphorus (P), zinc (Zn), magnesium (Mg), iron (Fe), copper (Cu), strontium (Sr), nickel (Ni), manganese (Mn), selenium (Se), chromium (Cr), molybdenum (Mo), cobalt (Co), lithium (Li), vanadium (V), aluminum (Al), lead (Pb), cadmium

(Cd), boron (B), barium (Ba), mercury (Hg), sulfur (S), germanium (Ge), silicone (Si), iodine (I), arsenium (As), and tin (Sn) were determined. Multi-elemental analysis was performed with inductively coupled plasma-atomic emission spectrometry (ICP-OES Optima 5300DV, Perkin Elmer, Massachusetts, USA). Using the same method, the level of 21 elements (Ca, Na, K, P, Zn, Mg, Fe, Cu, Sr, Ni, Mn, Cr, Mo, Co, Li, V, Al, Pb, Cd, B, and Hg) was determined in urine. The limits of detection were $< 1 \mu\text{g/L}$ for Zn, Sr, Ni, Mn, Se, Mo, Co, Li, V, Cd, B, Ba, Hg, Ge, As and Sn, $1\text{--}10 \mu\text{g/L}$ for K, Mg, Cu, Cr, Pb, Si and I and $10\text{--}50 \mu\text{g/L}$ for Ca, Na, P, Fe, Al, and S. The calibration curves were linear up to $100 \mu\text{g/L}$ for Cu, Sr, Ni, Se, Cr, Mo, Co, Li, V, Pb, Cd, Hg, Ge, Si, I, As and Sn, up to $1000 \mu\text{g/L}$ for Mn, B and Ba, and up to $10000 \mu\text{g/L}$ for Ca, Na, K, P, Zn, Mg, Fe, Al, and S. Relative standard deviation ranged from 0.32% to 2.19% for individual elements. Accuracy of the method was controlled with two certified materials (ICP Multi-Element Standard Solutions IV and VI) which were analyzed before each series of measurements and repeated every 30 samples. The strength of correlation was described with the value of a Spearman's rank correlation coefficient (R_s). Statistical significance was determined at $p < 0.05$. Statistica 7.1 software (Statsoft Inc., Oklahoma, USA) was used for the calculations. The methods were previously described in detail [19, 20].

Results

The mean (\pm standard deviation) age of the first episode of kidney stone disease in the studied group was 45.3 ± 16.1 years. The mean weight of the stone sent for analysis was 16.5 g (minimum 3, maximum 381.5). The mean volume of the 24-h urine sample was 1669 ± 336 ml. The most common components of all 219 analyzed stones were calcium oxalate ($58.6 \pm 37.62\%$) and calcium phosphate ($25.33 \pm 27.99\%$). Other components seen were uric acid ($11.76 \pm 29.95\%$) and magnesium phosphate ($4.28 \pm 12.19\%$). None of the stones contained cysteine, xanthine or 2,8-dihydroxyadenine.

The tables show the analysis of the correlations between the composition of the stones and the distribution of the elements in urine (Table 1) and between the composition of the stones and the distribution of the elements in hair (Table 2). The elements in the tables are listed according to their position in the periodic table. Only a few correlations at a moderate level of significance were found. They all were considered incidental. The authors also analyzed the correlations between the

levels of microelements in three biological materials, e.g. stones, urine and hair, and we made the following observations. The more that elements such as V, Pb, Hg, Ge, Si, I, and Sn were seen in the stones, the higher their level in hair; the more that Zn, Ni, Li, V, Al, and Pb were seen in urine, the higher their concentration in hair; and the higher the level of Mo, Co, V, Al, and Pb in urine, the more of these elements were found in the stones (data not shown). There were also 109 positive two-element correlations between two materials, i.e. when one element in one material correlated significantly positively ($R_s > 0$, $p < 0.05$) with another element in another material. Among them, the most common (more than 15 correlations) were observed for six elements listed according to the number of correlations: V, Al, Li, Pb, Co, and Mo. The content of the following pairs of elements in stones–hair was correlated with high statistical significance ($p < 0.001$): Fe–V, Fe–Ni, Cu–Ni, Cr–V, Mo–Co, Co–Ni, Co–V, Li–Mn, Li–V, V–Ni, V–Al, Cd–Ni, Cd–V, B–V, Hg–V, and Hg–Pb. Positive correlations for all samples (stones, urine, and hair) were established for only three elements: V–V, Pb–Pb, Pb–V, and Al–Pb (data not shown).

Discussion

Although the initial papers on trace elements in urinary stones were published in 1963 [21], 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 [4, 14, 22]. The results of many studies suggest that some elements including Ni, Mg, Al, Pb, Cd, and Cu together with other factors may affect the process of stone precipitation [12, 23]. On the other hand, most theories explaining the pathogenesis of stones formation do not include any role of trace elements. Special attention is generally paid to environmental, alimentary, occupational and socioeconomic factors [13, 24–26].

For the last 30 years, the analysis of microelements in biological samples has improved significantly in terms of precision, accuracy, reliability, and detection limits [8, 18, 27]. This study was focused on assessing the content of microelements in different biological materials that are known to contain detectable levels of different elements that may play some role in the process of urinary stone formation. The authors observed positive correlations of Sr and Zn concentrations in stones with calcium phosphate content ($R_s = +0.63$ and $+0.25$, respectively, $p < 0.001$) but not with calcium oxalate content ($R_s = -0.29$, $p < 0.0001$ and $R_s = +0.05$, $p = \text{NS}$, respectively). Durak et al., study-

Table 1. Correlation analysis between mineral composition of stones and distribution of elements in urine

Tabela 1. Analiza korelacji składu kamieni i składu pierwiastków chemicznych w moczu

Stone composition (Skład kamieni)	Elements in urine (Spearman's Rs) (Pierwiastki chemiczne w moczu)																				
	Li	Na	K	Mg	Ca	Sr	Cr	Mo	W	Mn	Fe	Co	Ni	Cu	Zn	Cd	Hg	B	Al	Pb	P
Calcium oxalates (Szczerwiany wapnia)	-0.01	+0.02	-0.02	+0.03	+0.11	+0.07	+0.16*	+0.01	-0.02	+0.02	+0.06	-0.02	+0.03	-0.06	+0.002	+0.02	-0.12	+0.08	+0.05	-0.13	+0.07
Calcium phosphates (Fosforany wapnia)	+0.04	-0.11	-0.05	+0.001	-0.04	+0.03	-0.08	-0.05	+0.01	+0.02	-0.03	+0.07	-0.02	-0.03	-0.06	+0.004	+0.02	-0.02	-0.06	+0.03	-0.08
Uric acid (Kwas moczowy)	-0.05	+0.08	+0.02	-0.03	-0.05	-0.13	-0.10	+0.02	-0.03	-0.04	-0.01	-0.08	-0.01	+0.10	+0.07	-0.01	+0.09	-0.06	+0.03	+0.08	+0.03
Magnesium phosphate (Fosforan magnezu)	+0.01	-0.15*	-0.07	+0.0003	-0.08	+0.02	-0.11	-0.01	-0.06	+0.0007	-0.05	-0.01	+0.004	+0.08	-0.08	-0.06	+0.03	-0.04	-0.05	+0.08	-0.09
Phosphate salts (Sole fosforanowe)	+0.03	-0.11	-0.04	+0.02	-0.05	+0.03	-0.08	-0.04	+0.01	+0.01	-0.04	+0.07	-0.01	-0.02	-0.08	+0.01	+0.02	-0.01	-0.05	+0.03	-0.06
Calcium salts (Sole wapniowe)	+0.03	+0.03	+0.01	+0.04	+0.10	+0.08	+0.16*	-0.03	+0.03	+0.03	+0.03	+0.06	-0.01	-0.13	-0.01	+0.06	-0.09	+0.07	+0.02	-0.12	+0.04

Spearman's rank correlation coefficient (Rs) is calculated for each pair of stone component correlation and element; * p < 0.05; # p < 0.01; + p < 0.001.

Tabela 2. Correlation analysis between mineral composition of stones and distribution of elements in hair

Tabela 2. Analiza korelacji składu kamieni i składu pierwiastków chemicznych we włosach

Stone composition (Skład kamieni)	Elements in hair (Spearman's Rs) (Pierwiastki chemiczne we włosach)																												
	Li	Na	K	Mg	Ca	Sr	Ba	Cr	Mo	W	Mn	Fe	Co	Ni	Cu	Zn	Cd	Hg	B	Al	Si	Ge	Sn	Pb	P	As	S	Se	I
Calcium oxalates (Szczaławiany wapnia)	-0.01	+0.05	+0.06	+0.01	-0.06	-0.12	-0.07	-0.10	-0.05	-0.03	-0.04	+0.08	+0.08	-0.03	-0.10	-0.06	+0.03	-0.11	-0.06	-0.004	-0.06	-0.06	+0.08	+0.05	+0.02	-0.05	-0.001	+0.001	-0.09
Calcium phosphates (Fosforany wapnia)	-0.02	-0.08	-0.13	+0.04	+0.07	+0.08	+0.09	+0.06	+0.11	+0.003	+0.06	+0.003	-0.04	-0.01	+0.09	-0.02	-0.02	-0.05	+0.02	+0.05	+0.02	+0.05	-0.04	-0.04	-0.03	+0.03	+0.03	-0.12	+0.07
Uric acid (Kwas moczowy)	+0.04	+0.03	+0.09	-0.03	-0.01	+0.06	-0.05	+0.004	-0.06	+0.01	-0.04	-0.07	-0.03	+0.03	-0.01	+0.06	-0.02	+0.17*	+0.11	-0.06	-0.01	+0.04	-0.001	+0.03	+0.002	+0.02	-0.08	+0.13*	-0.01
Magnesium phosphate (Fosforan magnezu)	-0.03	+0.04	-0.03	+0.004	+0.04	+0.08	+0.10	+0.12	+0.11	+0.04	-0.01	-0.13	-0.06	-0.10	+0.07	+0.002	-0.04	+0.02	+0.10	+0.04	+0.09	-0.02	-0.09	-0.02	-0.03	-0.03	+0.01	-0.07	-0.04
Phosphate salts (Sole fosforanowe)	-0.03	-0.07	-0.12	+0.03	+0.06	+0.07	+0.09	+0.06	+0.11	+0.004	+0.05	-0.01	-0.06	-0.02	+0.08	-0.02	-0.03	-0.04	+0.03	+0.06	+0.03	+0.03	-0.06	-0.04	-0.03	+0.02	+0.02	-0.12	+0.05
Calcium salts (Sole wapniowe)	-0.03	-0.05	-0.04	+0.03	-0.02	-0.10	-0.04	-0.10	-0.03	-0.06	+0.02	+0.13	+0.05	+0.005	-0.05	-0.07	+0.04	-0.17*	-0.14*	+0.04	-0.08	-0.02	+0.04	+0.01	+0.03	-0.01	+0.01	-0.08	+0.01

Spearman's rank correlation coefficient (Rs) is calculated for each pair of stone component correlation and element; * $p < 0.05$; # $p < 0.01$; + $p < 0.001$.

ing the distribution of Fe, Cu, Cd, Zn, and Mg in 47 stones and hair, found significant differences among the element levels in stones, patient hair, and control hair [14].

One of the most common trace element in the human body is Zn but the data concerning its role in lithogenesis is divergent. Some studies [22, 28] showed that low Zn levels in the urine of stone formers suggest its potential inhibiting action. Other data, however, shows increased excretion of Zn and Cu in stone formers or even no difference between stone formers and healthy populations [8, 29, 30]. There are studies showing that low concentrations of some elements like Mg, Mn and Zn in stones make them resistant to extracorporeal shock wave lithotripsy [31, 32]. The authors observed a negative correlation between Mg level and the content of calcium oxalate and uric acid (Rs values were -0.29 , $p < 0.001$; and -0.34 , $p < 0.001$, respectively). This finding supports the conclusions of some authors that Mg may act as an inhibitor of calcium oxalate stones [22]. This study also confirmed in a much larger group (5 vs. 219) the observation of Scott et al. about relatively low concentrations of Na in calcium oxalate stones and a high concentration of K and M in phosphate stones [12]. The analysis in Table 1 shows, that only one statistically significant positive correlation was observed between the concentration of Cr in urine and the content of calcium oxalate and calcium salts in stones ($p < 0.05$). This finding could prove the possible influence of Cr on lithogenesis; however the authors did not find supportive data in the literature, and it was therefore considered incidental and meaningless. The authors also observed a negative association between the concentration of Na in urine and magnesium phosphates in stones ($p < 0.05$), but the concentration of this element is highly diet-dependent because of its presence in food, table salt, and preservatives.

Increased scientific interest in trace elements has led to a search for reliable methods of quantifying and monitoring their levels in human body

tissues. Hair can be collected easily, non-invasively, and painlessly, and it accurately reflects body loads and human exposure to different contaminants, especially metals [17, 18, 33]. Hair structure contains a significant amount of cysteine, and some heavy metals (such as Pb and Hg) have a high affinity to sulfhydryl groups in this amino acid [17]. The main purpose of this study was to find the correlation between the levels of microelements in urine, stones, and hair and the mineral composition of the stones. Apart from the cognitive aspect, this correlation could also have practical application in cases in which the stone has been expelled and lost and cannot be examined. In cases such as this, an analysis of hair and/or urine could reveal, with some probability, the content of the stone and help in the prophylaxis of recurrence. Unfortunately, the obtained data (Table 2) does not allow for the creation of a proper and practical algorithm. With respect to hair, only Hg, B, and Se showed some weak correlation with uric acid and calcium salts. The analysis of the level of elements in urine and hair shows that when diet-dependent elements (Na, K) and those that are included in stones in high amounts (Ca, P) are excluded from investigation, the rest of the elements, mostly metals, can be detected in hair in several to several hundred times higher concentrations than they can be detected in urine (data not shown). However, significant variability in the profile of elements in hair is seen depending on the subject's age, sex, dietary habits, geochemical environment, hair color, smoking habits, and lifestyle [15, 16, 18]. Some authors even found significant inter-laboratory variations and concluded that standardization of testing methods is needed [34].

The authors concluded that although this investigation showed a correlation between the levels of some elements in the urine and hair and the chemical composition of stones, the authors were not able to create any practical algorithm to predict stone composition based on hair and urine analysis.

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