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ORIGINAL PAPER

Heavy elements in urinary stones

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Abstract The presence and role of heavy metals in urinary stones is debated. We investigated the distribution of trace heavy metals in 78 calculi of well-defined composition by means of microfluorescence X analysis using synchrotron radiation. Seven elements were identified, the most abundant being Zn and Sr which together accounted for 91% of the heavy metal content of stones. The other heavy metals were Fe, Cu, Rb, Pb and Se. Zn and Sr were virtually confined to calcium-containing stones, whereas only trace amounts were found in uric acid or cystine stones. Among calcium stones, Zn and Sr were more abundant in calcium phosphate than in calcium oxalate stones and, in the latter, in weddellite than in whewellite stones. Fe, Cu and Rb were much less abundant and also found mainly in calcium stones. Pb was significantly less abundant than in previous studies, thus suggesting a rarefaction of Pb in the environment, and appreciable amounts of Se were found only in cystine stones. In conclusion, the preponderance of Zn and Sr, both bivalent ions, in calcium-containing stones suggests a substitution process of calcium by metal ions with similar charge and radius rather than a contribution of the metals to stone formation. Further studies are needed to examine the relationships between urine concentration in calcium or other solutes and the amount of Zn and Sr in calcium stones.

Keywords Heavy metals · Microfluorescence X · Synchrotron radiation · Calcium oxalate · Calcium phosphate

Introduction

Urolithiasis constitutes a serious health problem that affects 3–20% of the population, depending on the geographical region. Calculi are composed of various inorganic and/or organic compounds. Calcium oxalate (70% of the cases), calcium and magnesium phosphates (15%), uric acid (10%) and cystine (1%) are the main common components [1]. All but cystine are organized in various crystalline phases: whewellite and weddellite for calcium oxalate; carbapatite, brushite, octacalcium phosphate, whitlockite and struvite for calcium and magnesium phosphates, anhydrous and dihydrate forms for uric acid.

In addition, trace amounts of heavy metals have been found in urinary calculi. Their role in lithogenesis is debated [2–7]. They may be involved in crystal induction, depending on the particular relationships between metals and solutes able to crystallize in urine. Some authors reported a higher metal content in the core than in peripheral layers of stones, thus suggesting a possible lithogenic effect of heavy metals [2, 3]. Indeed, as metals such as Mg [4], Zn or Al [5, 6], or Fe^{3+}-citrate complexes [7], have

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been shown to act as inhibitors of calcium oxalate growth at very low concentrations, it may be hypothesized that other metals may also promote or, conversely, inhibit crystal nucleation or growth of mineral or organic species involved in urinary calculi. Another possibility is a non-specific capture of metals excreted in urine during the time the stone was present in the urinary tract.

Few studies to date have investigated the heavy metal content in urinary calculi by physical methods [8–13] and even fewer provided as to information the relationships between metals and crystalline phases. Moreover, among the data available from various research groups throughout the world, large discrepancies appear as concerns both the presence of metals and their amount in urinary calculi. The goal of our study was to investigate by precise techniques based on synchrotron radiation the heavy metal content of calculi collected in France, and to examine the possible relationships between these heavy metals and crystalline phases of stones.

Materials and methods

Seventy eight urinary stones from French patients referred to our laboratory between 1991 and 2004 were first characterized by morphological examination associated with infrared spectrophotometry using a Fourier transform infrared spectrometer Vector 22 (Bruker Spectrospin, Wissembourg, France) according to the analytical procedure previously described [14, 15].

These stones were further investigated by μ-Synchrotron Radiation X-ray Fluorescence (μ-SRXF) at LURE (Laboratoire d'Utilisation des Rayonnements Electroniques, Orsay, France) in order to identify and quantify heavy metals ($Z > 20$). The X-ray microprobe [16] was implemented on a bending magnet of the DCI storage ring (1.85 GeV, 300 mA) using a graphite double crystal and Bragg Fresnel multilayer lens (BFML) to transform the initial white beam into a monochromatic and partially focused bundle of X-rays (X-ray photons with energies close to 15.5 keV). The diameter of the focal spot was set by the input pinhole to 20 μm. The X-ray signals from the sample were recorded by means of a Si(Li) detector (Fig. 1). All elements of interest, starting from potassium, could be detected in such conditions. For each stone, at least three measurement points were examined from the core to outer layers in order to assess the zonal distribution of metals. Results are expressed as the mean metal content for each group of stones. The biological samples were not polished, a preparation step that would have been required to obtain absolute quantitative measurements. Indeed, due to the large range of levels for each metal and because the results are the mean of several measurements for each stone, an absolute quantification is not relevant. Intergroup comparison were performed by ANOVA. Results are presented as mean ± standard deviation.

Results

Seven heavy metals have been identified in the stones: Fe, Zn, Cu, Sr, Rb, Se, Pb. The content ranged from only some ppm for Se to 0.2% for Zn. The results are summarized in Table 1. Among the panel of 78 stones, the range of levels for each metal was as follows: from 4 to 87 ppm for Fe; from 1 to 11 ppm for Cu; from 2 to 2026 ppm for Zn; from 0.02 to 20 ppm for Rb; from 0.7 to 539 ppm for Sr; from 0.1 to 70 ppm for Pb; and from 0.2 to 3.6 ppm for Se. As shown in Table 1, striking differences in the mean metal content were observed according to the main crystalline phase of stones.

Calcium stones and non-calcium stones

The global amount of heavy metals was significantly greater in calcium stones than in non-calcium stones. The

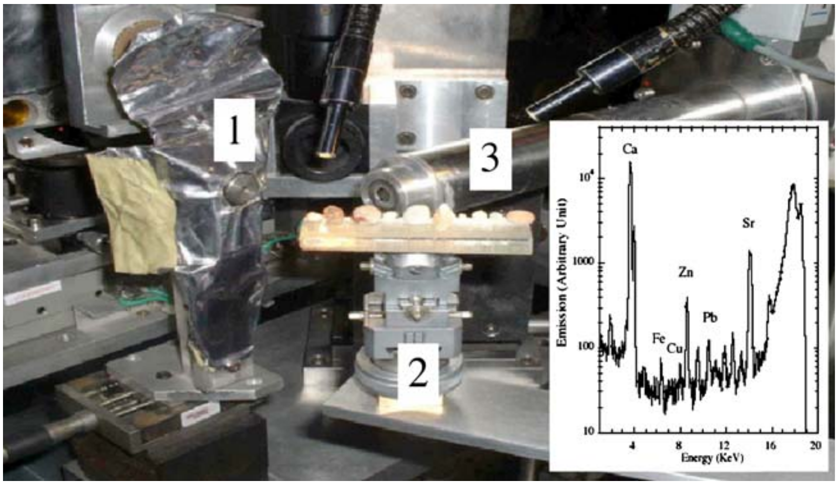

Fig. 1 Photograph of D15 experimental station. The incident beam (*1*) coming from a pinhole is directed to the sample (*2*). X-ray signals from the sample were registered by the use of a Si(Li) detector (*3*). In the *inset*, the contribution of various elements in the emission spectra signals of the following elements can be seen

Table 1 Heavy metal content of urinary stones (ppm)

Main component	Nombre	Fe	Cu	Zn	Se	Rb	Sr	Pb
Calcium stones	43	35 ± 43	5 ± 7	525 ± 768	1 ± 0.5	7 ± 12	239 ± 300	19 ± 27
Calcium oxalate	19	32 ± 26	4 ± 4	95 ± 176[b, d]	1.5 ± 0.5	2 ± 5	74 ± 56[b, d]	12 ± 9
Whewellite (Wh)	15	33 ± 22	5 ± 4	42 ± 38[d]	1.5 ± 0.5	2 ± 5	61 ± 41[d]	12 ± 10
Pure	5	31 ± 19	4 ± 4	41 ± 19	1.5 ± 0.5	4.5 ± 8	81 ± 48	11 ± 5
Wh + UA	6	26 ± 14	8 ± 3	15 ± 5	1.5 ± 0.3	0.5 ± 0.3	33 ± 14	8 ± 5
Wh + Wd	4	45 ± 31	2 ± 0.5	85 ± 46	1.5 ± 0.5	1.5 ± 2.5	75 ± 36	18 ± 18
Weddellite (Wd)	4	29 ± 43	1 ± 1	290 ± 346	0.7 ± 0.2	0.5 ± 0.4	125 ± 82	14 ± 4
Calcium phosphate (CaP)	24	38 ± 53	6 ± 9	865 ± 882	0.9 ± 0.4	11 ± 14	370 ± 349	25 ± 35
Carbapatite (CA)	18	44 ± 60	7 ± 11	1059 ± 934	1 ± 0.5	14 ± 14	455 ± 364	31 ± 39
CA + Ca oxalate	8	68 ± 83	7 ± 11	1419 ± 1118	1 ± 0.5	7 ± 16	350 ± 181	62 ± 39
CA + Wh	4	87 ± 112	3 ± 3	813 ± 387	1 ± 0.3	12 ± 23	367 ± 223	70 ± 46
CA + Wd	4	50 ± 49	11 ± 15	2026 ± 1337	1 ± 0.5	2 ± 0.6	332 ± 161	54 ± 36
CA + MAP	10	25 ± 24	7 ± 11	770 ± 694	1 ± 0.5	20 ± 11	539 ± 456	6 ± 11
Brushite (Br)	6	18 ± 15	2.5 ± 1	284 ± 263[c]	1 ± 0.2	3 ± 6	117 ± 70[c]	6 ± 4[c]
Non-calcium stones	35	6 ± 5[f]	2.5 ± 5.5	33 ± 72[f]	1 ± 1.2	1.5 ± 3[e]	24 ± 52[f]	1 ± 3[f]
MAP	7	6 ± 7	1 ± 0.5	141 ± 111[c]	0.2 ± 0.1	6 ± 5	108 ± 70	3 ± 7
Uric acid (UA)	23	6 ± 5	1.5 ± 1	4 ± 3	0.3 ± 0.1	0.1 ± 0.1	4 ± 5	0.8 ± 0.7
UAA + UAD	5	4 ± 2	2 ± 0.5	2 ± 1	0.4 ± 0.3	0.1 ± 0.1	1 ± 1	0.2 ± 0.2
UAA + Wh	18	6 ± 6	1 ± 1	5 ± 3	0.2 ± 0.1	0.1 ± 0.05	5 ± 5	1 ± 0.7
Cystine	5	6 ± 6	3 ± 2	11 ± 4	4 ± 1.3[c, g]	0.02 ± 0.02	0.7 ± 0.7	0.1 ± 0.1

[a] $P < 0.05$; [b] $P < 0.0001$ vs calcium phosphate [c] $P < 0.01$; [d] $P < 0.0001$ vs CA [e] $P < 0.01$; [f] $P < 0.0001$ vs calcium stones [g] $P < 0.01$ vs Wh

proportion of Zn and Sr was especially high in calcium phosphate and to a lesser extent in calcium oxalate stones, but Fe, Rb and Pb were also more abundant in calcium stones when compared to struvite, uric acid or cystine stones. The highest proportion of the heavy metals in calcium stones was observed for Zn (mean ± SD 525 ± 768 ppm), followed by Sr (239 ± 300 ppm), Fe (35 ± 43 ppm) and Pb (19 ± 27 ppm). Other metals accounted for less than 10 ppm on average.

Among calcium stones, calcium phosphate calculi contained the highest proportion of metals, especially Sr and Zn, when compared to calcium oxalate stones ($P < 0.001$). Struvite stones, all of which contain some proportion of calcium phosphate, particularly carbapatite, had a higher content of heavy metals, particularly Sr and Zn, than did uric acid or cystine stones. Uric acid stones were especially poor in heavy metals. Se content was significantly higher in cystine stones than in all other types of calculi, whereas the content in Pb and Rb was especially low in cystine stones and in uric acid stones as well. No significant difference in the heavy metal content was observed in core versus outer layers of the stones.

Metal content according to the main crystalline phase

Within a given chemical type of stones, heavy metal content differed according to the crystalline phase. Among calcium phosphate calculi, Sr, Zn and Pb were significantly less abundant in brushite than in carbapatite stones ($P < 0.01$). Among calcium oxalate stones, Zn was more abundant in weddellite than in whewellite. The same was true for Sr but not for Fe, Cu or metals found in very low proportion such as Se and Rb.

Discussion

Our study was aimed at assessing the content of trace metals in urinary stones recorded in the recent period. Three main findings emerge from our data. First, overall, urinary stones contain discernible amounts of heavy metals, especially Zn and Sr; second, appreciable amounts are found only in inorganic phases, i.e., calcium oxalate, calcium phosphate and struvite (which always contain some amount of calcium phosphate), whereas only very small amounts are found in organic phases (uric acid and cystine stones); third, within calcium-containing stones, calcium phosphate contain greater amounts of trace metals than do calcium oxalate, and within calcium oxalate, weddellite retains more trace metals than whewellite. In addition, we observed that selenium is present in measurable amounts only in cystine (sulfur-containing) stones.

That heavy metals, especially Zn and Sr, incorporate to a strikingly greater extent in calcium-containing stones than in non-calcium stones was also reported by other authors [8, 9, 11]. In our study, the content of Zn was nearly 15 times higher, and the content of Sr nearly 10 times higher in calcium than in non-calcium containing stones. Similarly, Levinson [9] observed a considerably higher amount of Zn and Sr in calcium oxalate, calcium phosphate and struvite stones than in uric acid and cystine stones, and an even more marked difference was reported by Joost et al. [11].

According to Goldschmidt's rules, differences in the heavy metal content between calcium and non-calcium stones may be explained by the similarity between the ion charge and size of Zn and Sr and calcium, which allows these elements to substitute to calcium in the crystal lattice [17]. Thus, divalent metal ions such as Zn and Sr are likely the most prone to incorporate into calcium-containing stones.

Among calcium stones, we found a significantly greater content of Zn and Sr in calcium-phosphate (especially carbapatite) than in calcium oxalate stones. Levinson et al. [9] observed a 2–4 times greater Zn and Sr content in carbapatite than in weddellite and whewellite stones, and a similar observation was also made by Joost et al. [11].

Apatite has been shown to easily incorporate various metals, and is used as a sorbent for radionuclides such as uranium [18] and heavy metals [19, 20], which may be included in the apatite structure through a substitution process. Indeed, calcium ions which, in apatite, occupy two non-equivalent sites M(1) and M(2) in the crystal lattice, may be substituted by other metals according to their radius. Here, the proportion of heavy metals in apatite crystals may depend on the ratio metal/metal+calcium in the medium as suggested by Zhu et al. [21]. Accretion of heavy metals on apatite particules may also be favored by the small size of apatite nanocrystals (about 10 nm) whereas all other crystalline species found in urine are about 100 nm in size. For a given mass, the absorptive capacity of nanoparticles is always higher than that of the bulk material [22–24]. Moreover, hydrated areas are present at the surface of apatite nanocrystals and may contain exchangeable ions. Of note, brushite whose structure differs from that of apatite retains a lesser amount of heavy metals.

Within calcium oxalate stones, Zn and Sr content was higher in weddellite than in whewellite stones in our series. Other authors similarly found a nearly twice higher content of Zn and Sr in weddellite than in whewellite stones [9, 11]. Levinson et al. [9] suggested that phase conversion from weddellite to whewellite, a more stable crystalline form of calcium oxalate, may result in the release of heavy metals in the medium. However, in our series, only Zn and Sr were found in lower amounts in whewellite than in weddellite stones, whereas no significant differences were noted for the other trace metals. Thus, phase conversion probably is not the only mechanism involved. The Ca/Sr ratio was significantly greater in whewellite than in weddellite stones (3,376 ± 1,874 vs. 1,509 ± 815, $P < 0.05$) and was lowest in carbapatite stones (939 ± 493, $P < 0.05$ vs. whewellite stones). The same was found for the Ca/Zn ratio, which was significantly higher in whewellite than in weddellite stones (7,622 ± 6,941 vs. 1,914 ± 1,084, $P < 0.01$). Indeed, strontium is known as a common substituent of calcium in apatite [17], Thus, it is not surprising to find a lower Ca/Sr ratio in carbapatite-rich calculi. Of more interest is the difference in the Sr content between whewellite and weddellite stones. The latter were shown, contrary to whewellite ones, to develop mainly in hypercalciuric states [25, 26]. An hypothesis is Sr content could be a marker of hypercalciuria. Indeed, as shown by metabolic investigations, Sr and calcium seem to have a similar behaviour in our metabolism. As a matter of fact, significant relationships exist between intestinal and renal handling of calcium and the Sr level in biological fluids, thus suggesting the potential interest of Sr as a marker of intestinal absorption and renal excretion of calcium [27, 28]. As for whewellite, it may crystallize in another biochemical environment than weddellite, namely in hyperoxaluric states and especially in urine where the calcium/oxalate ratio is low [29].

Differences in heavy metal content of urine are also informative. For example, Zn is common in the body compared to copper. Thus, the mean Zn excretion in urine is about 20 times higher than that of Cu [30]. Interestingly, calcium stones contain about 200 times more Zn than Cu while in non-calcium stones, the Zn content is low (6 ± 3 vs. 525 ± 768 ppm in calcium stones, $P < 0.0001$) and the ratio Zn to Cu also is low at about three. From these results, we can deduce that Zn is preferentially incorporated in calcium salts while the Cu content does not significantly differ between calcium and non-calcium stones.

Zn and Sr content in mixed stones reflected the proportion of the respective phases within the stone. For example, mixed calcium oxalate/uric acid stones contained intermediate amounts of heavy metals. At variance with Perk et al. [3], we found no difference in the heavy metal content in the core versus outer layers of the stone, irrespective of the crystalline phase. This suggest that heavy metals do not play a role in the induction of stones.

With respect to Fe, all studies including ours found a much lower content in non-calcium than in calcium-containing stones, without significant differences between whewellite, weddellite or carbapatite stones. The higher Fe content could result from the inhibitory properties of Fe^{3+} on calcium oxalate crystallization as suggested by Meyer and Thomas [7] and more recently by Munoz et al. [31]. The presence of Fe in calcium oxalate stones may result from a trapping of Fe ions at the crystal surface or in the crystal lattice.

We found selenium in only trace amounts (less than 2 ppm) in all types of stones, with the exception of cystine stones which contained about 4 ppm. A similarly low Se content in stones was also found in other studies [9, 11] but Se content was not determined in cystine stones in these studies. The presence of Se in appreciable amounts in cystine stones, the only sulfur-containing stones, is in keeping with the vicinicity of Se and S in terms of atomic mass and biological properties. Accordingly, Se may substitute for S, to form Se-cystine as previously reported [32].

Pb was found in higher amounts in calcium-containing stones than in organic phases, as it was virtually absent from uric acid and cystine stones in our series as in other studies [9, 11]. Of note, we found a much lower amount of Pb in calcium stones in our series, which included stones referred over the recent decade, than in the studies of Levinson and Joost, which analyzed stones formed 20–30 years earlier. The reduction of Pb in the current study compared to historic data suggests a role for changes in environmental concentrations of Pb. As a matter of fact, lead pollution decreased in industrialized populations over the recent decades as suggested by the lower Pb content found in blood among the French population [33], due to the progressive replacement of lead water pipes by polyvynyl chloride pipes in our towns and by the suppression of lead-containing house painting. Such a variation with time was not observed for any of the other trace metals analyzed.

Conclusion

Appreciable amounts of heavy metals in stones were only found for the divalent Zn and Sr ions and, to a lesser extent, for Fe, whereas Rb, Cu, Se and Pb were found in negligible amounts. In addition, Zn, Sr and Fe ions were found almost exclusively in calcium-containing stones, and more in phosphate than in oxalate stones. Incorporation of Zn and Sr in calcium stones is likely to result from the similarity in ion charge and radius with calcium, favoring a substitution process of calcium by metal ions rather than a contribution to stone formation. Further studies should examine possible relationships between urine concentration in calcium or other solutes and the amount of Zn and Sr in calcium stones.

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