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Rare-earth elements in urinary calculi

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Summary. In vitro studies have demonstrated that trace elements have inhibitory as well as stimulatory effects on the crystallization of urinary stones. Little is known about the activities of rare-earth elements (REEs) in the human body. Although their physiological role is unclear, an effect on calcium transport mechanisms is discussed. In the present study, ten kidney stones (six oxalate and four phosphate stones) were analyzed by neutron-activation analysis for their REE patterns. Urinary stones are capable of concentrating these elements, and some fractionation into light and heavy REEs appears to take place during deposition. Significantly elevated concentrations of heavy REEs such as europium, terbium, and lutetium were detected in phosphate stones as compared with oxalate stones ($P<0.005$).

Key words: Urolithiasis – Rare-earth elements – Neutron-activation analysis

A broad spectrum of techniques have been employed to obtain information on the process and conditions of urinary stone formation. In addition to the well-known major components, much attention has been paid to trace elements, which participate in a variety of metabolic processes in the human body. Using plasma atomic emission spectroscopy, the urine and serum of active stone formers have been demonstrated to contain significantly lower levels of nickel, manganese, lithium, and cadmium [12].

Inhibitory as well as stimulatory influences on the crystallization process of calcium oxalate stones by metallic ions have been documented in vitro [3, 6, 11, 26]. Rare-earth elements (REEs; atomic numbers 58–71 lanthanide series) can be utilized to infer chemical fractionation processes in natural systems. They are used as an indicator for geochemical fractionation or crystallization processes and are known to have lithophilic properties [17]. In solution and with suitable ligands, they are capable of forming a variety of extremely stable, insoluble complexes. Furthermore, evaluation of REE patterns is recognized as being important in determining the behavior of biological materials. Their levels are significantly lower in biological materials than in terrestrial samples; i.e., at or below the nanogram per gram (parts per billion) level they are generally higher in plants than in animals.

Few data are available on REEs in human samples, and their physiological activities remain largely unclear. A role in calcium-transport mechanisms is discussed. The aim of the present study was to obtain information on a possible role of REEs in the etiology of urolithiasis by evaluating their concentrations in calcium oxalate and phosphate stones. Investigations were performed using instrumental neutron-activation analysis (INAA) [16] and chondrite normalization, a standard geochemical procedure for studying REE patterns [10].

Materials and methods

Sample preparation

Ten kidney stones with their mineralogical composition established by X-ray diffraction – i.e. six calcium oxalate stones, three calcium phosphate stones, and one struvite (magnesium-ammonium phosphate) stone – were selected for INAA. They were rinsed with deionized water, and 200 mg of the dried samples was used for analysis. Biological standard materials animal bone, (IAEA H-5) and orchard leaf (NBS SRM 1571) were used as controls.

Analytical procedure

Samples were irradiated for 8 h in a TRIGA Mark II reactor at a neutron flux of about 2×10^{12} neutrons cm^{-2} s^{-1}. After a cooling period of 1 day, samples were decontaminated. Subsequently, four counting cycles were performed using high-resolition, high-purity germanium detectors and a gamma spectroscopy system: cycle 1 (lasting 2–5 h) was started 30 h after the end of irradiation; cycle 2

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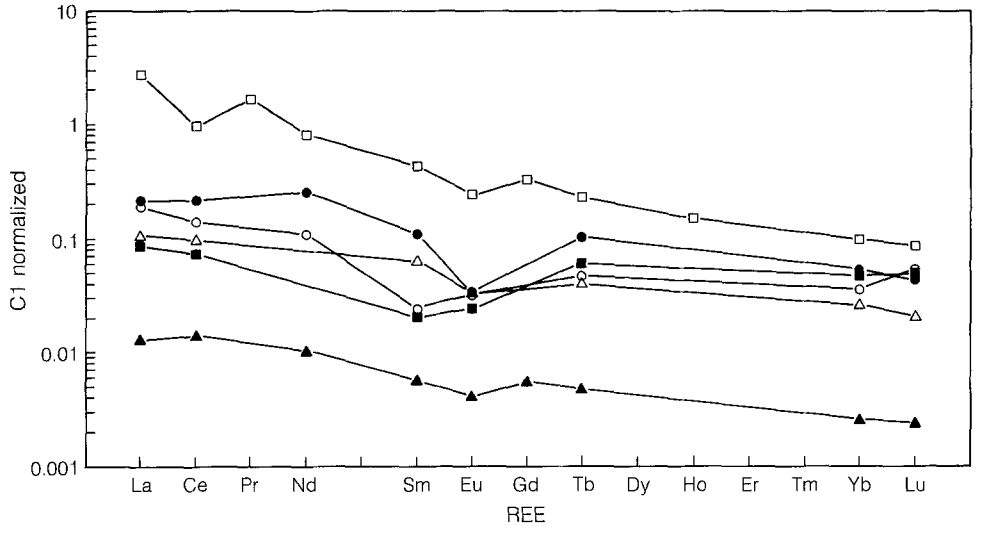

Fig. 1. REE distribution in oxalate stones as compared with biological standard materials (orchard leaf, animal bone); —●— oxalate (Ni2); —▲— animal bone; —△— oxalate (Ni3); —○— oxalate (Ni5); —□— orchard leaf; —■— oxalate (Ni7)

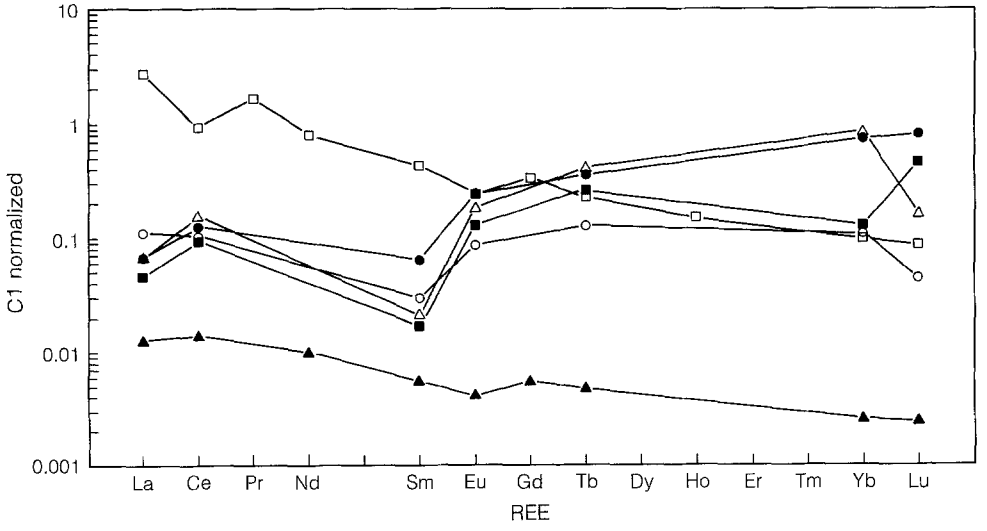

Fig. 2. REE distribution in phosphate stones as compared with biological standard materials (orchard leaf, animal bone); —△— apatite (Ni1); —▲— animal bone; —○— struvite (Ni4); —●— apatite (Ni9); —□— orchard leaf; —■— apatite (Ni10)

Table 1. REE content of urinary stones as determined by INAA

	Phosphate stones ($n = 4$)	Oxalate stones ($n = 6$)
Lanthanum (La)	0.027 ± 0.010	0.059 ± 0.0200
Cerium (Ce)	0.115 ± 0.026	0.124 ± 0.047
Neodymium (Nd)	0.135 ± 0.129	0.095 ± 0.011
Samarium (Sm)	0.007 ± 0.005	0.010 ± 0.007
Europium (Eu)	0.014 ± 0.006[a]	0.003 ± 0.007[a]
Gadolinium (Gd)	0.200 ± 0.115[a]	0.073 ± 0.023[a]
Terbium (Tb)	0.016 ± 0.007	0.002 ± 0.003
Thulium (Tm)	0.062 ± 0.043	0.046 ± 0.029
Ytterbium (Yb)	0.116 ± 0.102	0.024 ± 0.033
Lutetium (Lu)	0.014 ± 0.013[a]	0.002 ± 0.004[a]

Data represent mean values ± SD expressed in ppm
[a] $p < 0.005$; student's t-test

was begun 4 days thereafter, followed 5 days later by cycle 3 (10–40 h each); and cycle 4 (30–60 h) was initiated 15–20 days after the completion of cycle 3. The analytical procedure has been described in detail elsewhere [15, 17]. The final data for isotopes were obtained by averaging the data on the several counts and those on the different gamma lines within each count.

Results

Figures 1 and 2 show the chondrite-normalized REE data obtained for oxalate and phosphate stones, respectively; both data sets were compared with two standard biological materials (orchard leaf and animal bone).

The comparative data obtained are given in Table 1. In both oxalate and phosphate stones, REE levels were between the values recorded for the two controls, i.e., they were markedly higher as compared with the levels measured in animal bone but did not reach those detected in plants. Both stone types showed very low amounts of samarium. Elevated levels of europium, terbium, and lutetium were found ($P < 0.005$, Student's t-test) in phos-

phate stones as compared with oxalate stones; this enrichment of the heavier lanthanides yields a REE pattern distinctly different from that observed in oxalate stones (Table 1).

Discussion

The content of trace elements in urinary stones appears to be more than a reflection of dietary and environmental factors. No difference was found in the composition of stones of the same type in a comparison of three separate areas in the United States [19]. Stones containing calcium phosphate (apatite phase) tend to concentrate some elements – such as zinc, tin, and lead – to a greater extent than do calcium oxalate stones, but none of these affect the growth of calcium crystals at concentrations approximating those found in urine [21].

On the basis of INAA, lower concentrations of alkaline metals have been reported in oxalate stones, but the role of these elements in stone formation continues to be unclear [23]. Elsewhere, atomic absorption spectroscopy has revealed no correlation of trace-element levels – with the exception of zinc – in stones, blood, and urine [13]. In earlier reports it has been suggested that the presence of REEs in microorganisms is a simple surface phenomenon due to passive attachment to the cell surface rather than a reflection of intracellular transport mechanisms [1].

REEs are made available to the food chain through rain seeping into the groundwater and through atmospheric dust. They enter the body via ingestion and inhalation and are excreted via both feces and urine. The organ distribution of physiologically available REEs appears to be relatively constant. The liver and skeleton show most of the activity, hepatic sequestration being much more labile than skeletal uptake. This difference in organ retention may reflect extracellular deposition in the inorganic bone matrix as compared with cellular association of hepatic lanthanides. Moreover, recent studies have shown a tendency for lighter REEs to accumulate in the liver and heavier REEs, in bones, indicating selective deposition, with some fractionation possibly taking place within the body [18]. This finding contrasts with initial suggestions that REEs are not fractionated during the absorption of plants by animals and humans following the finding of similar REE patters in animal bone, bovine liver, human hair, and orchard leaf. In many cases, however, only few REEs were measured; thus, the overall REE patterns could not be evaluated [7].

Few reports in the literature have dealt with REEs in human samples. Higher REE levels have been documented in a variety of tissues, such as the corneal stroma, the lungs of industrial workers, the spleens of alcoholics, and infarcted cardiac tissue [4, 8, 22, 27]. Elevated levels have also been demonstrated in patients with rheumatoid arthritis, which may have to do with the supposed anti-inflammatory properties of REEs, as they have the capacity to suppress mitogen- and antigen-induced lymphocyte proliferation [5, 28].

Although the physiological role of REEs is unknown, they have recently attracted increasing interest as isomorphic competitors for calcium-binding sites in biological systems. On human platelets, lanthanides are capable of blocking receptor-operated Ca^{2+} channels and thus inhibit Ca^{2+} influx into the cytosol [20]. In animal models, systemic and topical lanthanum treatment produces a decrease in contact hypersensitivity and epidermal Langerhans-cell density by altering calcium transport across the cell membrane [2]. Monomer-type crystalline Ca^{2+}-adenosine triphosphatase (ATPase) aggregates can be induced by lanthanides in sarcoplasmic reticulum vesicles [25]. In enzymatic processes, lanthanide ions have been found to substitute for Ca^{2+} on muscle phosphorylase-kinase in activating this enzyme to about 60% [24]. Lanthanides have also been found to bind in vitro with high affinity to vitamin D-dependent intestinal calcium-binding protein [9].

Moreover, crystal-chemical experiments have shown that natural apatites form a more resistant complex when they are treated with lanthanides. In healthy and carious dental enamel, treatment with a Ce(III)-nitrate solution resulted in an increase in the concentration of Ce^{3+}, which replaced the Ca^{2+} in Ca^{2+}-apatite to form a mineralogically harder Ce^{3+}-apatite complex [14].

Our finding of elevated heavy REE levels in phosphate stones indicates a concentration mechanism similar to that occurring in natural (nonbiogenic) apatites. A certain decrease in samarium was also noted, which is not observed in nonbiogenic samples but has previously been observed in tissue samples [7, 22]. The metabolism of REEs in the human body is not well understood. The distribution of minor and trace elements as well as of REEs reflects the composition of urine during stone formation. The use of INAA enables assessment of the elemental composition of individual stones. The role of REEs in interfering with chemical fractionation processes in natural systems is unclear. Urinary stones apparently act as traps for some elements and are capable of concentrating REEs due to their slow accumulation process. As compared with the characteristic REE patterns seen in plants, some fractionation into light and heavy REEs appears to take place during the deposition of oxalate and phosphate stones.

Evaluation of REE patterns in urinary stones could shed some light on the issue of stone initiation by addressing the question as to whether nucleation is heterogeneous. It is unknown whether the presence of REEs in urinary stones is simply a result of external deposition from the urine or whether these elements play a role in the metabolism of calcium-transport mechanisms in tubular cells and thus affect stone formation. Further studies on REE concentrations in the serum and urine of stone formers as compared with normal controls could shed some light on this question.

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