

Strontium overload and toxicity: impact on renal osteodystrophy

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Abstract

Although the prevalence of aluminium-related bone diseases has declined, osteomalacia still persists at a low prevalence. The redistribution of bone disease prevalence corresponds to evolving regimens in the treatment of renal disease. Studies have demonstrated an association between the accumulation of strontium in bone and the presence of osteomalacia. The uptake of strontium has been shown to be dose-dependent, with distribution mainly in newly formed compact and cancellous bone. Animal studies demonstrated that high doses of strontium induced alterations of mineralization and, in a rat model of chronic renal failure, high strontium doses induced mineralization defects, with a corresponding 160-fold accumulation of strontium in bone. Studies indicated that the accumulation of metals in bone might be synergistic. Aluminium bone content was shown to be higher when both aluminium and strontium were administered compared with when only strontium was given. Studies in dialysis patients demonstrated that strontium levels and strontium/calcium ratios were elevated in the bone of osteomalacia patients compared with other types of renal osteodystrophy. In certain dialysis centres of developing countries, high strontium levels present in dialysis fluids correlated with strontium serum content. At these centres, the use of acetate-based concentrates may have been the source of strontium-contaminated dialysis fluids. In a recent study of bone biopsies taken from patients of French dialysis centres, strontium content was increased in bone of osteomalacic patients compared with other bone diseases and with controls. Several other trace elements have been found to accumulate in the bone of uraemic patients, with significant concern regarding associated pathology. Environmental and medical exposure to such trace metals should be evaluated to establish toxic thresholds and to eliminate the possibility of associated renal osteopathies.

Keywords: dialysis; osteomalacia; osteoid; strontium; trace element

Introduction

Strontium, a divalent cation with a molecular weight of 87.62 Da, ranks 15th in order of element abundance in the Earth's crust, with a concentration of 450 p.p.m. Strontium is the most abundant trace element in ocean water, reaching levels of 8 mg/l. Concentrations in rivers and springs are much less, ranging from 0.021 to 0.375 mg/l. Food and beverages represent the main environmental sources of strontium. Foods such as cereals, grains and seafood may contain up to 25 mg/kg of strontium [1]. Exposure may also result from contaminated phosphate binders and the use of parenteral and dialysis fluids containing strontium [2,3].

Strontium enters the body primarily through the gastrointestinal tract; it is also absorbed to a lesser degree by the lungs and skin. The normal kidney eliminates the majority of the absorbed element, although strontium is also excreted to a much lesser extent in faeces and sweat. Because the kidney is the primary source of strontium elimination, patients with renal insufficiency are at an increased risk for accumulating this metal. Strontium accumulates almost exclusively in the bone, with bone deposition representing >99% of the total body burden. Strontium concentrations are also elevated in the serum of uraemic patients—up to 30-fold higher than in individuals with intact renal function [1].

Strontium and calcium are remarkably similar in the way that the body handles them; they are both absorbed in the gastrointestinal tract, concentrated in the bone and excreted primarily in the urine. Strontium is absorbed from the gut by the same mechanisms used for calcium, and one mechanism of strontium incorporation into bone involves ionic exchange with bone calcium. Both elements are reabsorbed by the renal tubules during elimination, although renal discrimination, highly in favour of calcium, accounts for

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significantly greater strontium elimination [4]. Moreover, studies on strontium kinetics historically have been carried out in connection with calcium, demonstrating a unique interaction between strontium and calcium. Thus, the use of certain calculated values used to describe strontium behaviour, such as the 'observed ratio', underscores the similar involvement of these two elements in a number of biological processes [1].

Several trace elements accumulate in the bone of patients with renal failure; these include aluminium, cadmium, chromium, copper, fluoride, iron, lanthanum, lead, strontium and zinc [2,5–9]. Some of these trace elements are suspected to cause mineralization defects. Indeed, renal osteodystrophy has been associated with a number of these trace elements. For example, D'Haese *et al.* found increased concentrations of bone aluminium and strontium associated with osteomalacia [8]. Bone biopsies reveal that bone strontium levels, as well as strontium/calcium ratios are increased in patients with osteomalacia compared with individuals with normal bone histology, and in comparison with all other types of renal osteodystrophy [3]. However, further research is needed to assess the association of strontium with mineralization defects.

Clinical implications: renal osteodystrophy

The prevalence of renal bone disease has shifted within the last three decades in response to evolving therapies for patients with end-stage renal disease (ESRD). Hyperparathyroid bone disease (osteitis fibrosa) still predominates in chronic haemodialysis patients, although with less severity. Among low turnover uraemic osteodystrophies, adynamic bone disease has been reported with greater frequency than in prior studies, and prevalence of osteomalacia has fallen [10]. These changes in renal osteodystrophy have occurred with the introduction of aluminium-free phosphate binders and vitamin D analogues, and in conjunction with vigilant efforts to reduce aluminium intake through diet and dialysate. Although aluminium intoxication has decreased, osteomalacia persists in Western countries at a prevalence of 3–5% [11]. The situation is very different in developing countries, where aluminium intoxication and an associated osteomalacia are more prevalent [3]. Patients with osteomalacia suffer from severe bone pain, bone deformities and fractures [10].

Several other metals have been implicated in the development of osteomalacia. In dialysis patients, bone concentrations were increased for metals including chromium, zinc, tin and strontium, regardless of water treatment or country [8]. Other potential causes of osteomalacia are vitamin D deficiency, uraemic toxins, metabolic acidosis, hypocalcaemia, Fanconi syndrome and phosphate depletion in the context of hypophosphataemia [10].

Strontium accumulates in bone

It has been generally accepted that strontium is taken up into bone over two phases: a relatively rapid uptake into new bone and a long-term process of exchange in the old bone. Strontium is incorporated into bone by surface exchange or ionic substitution mechanisms. However, strontium is not deposited in osteoid tissues [12]. The uptake of strontium has been shown to be dose-dependent, with heterogeneous distribution in newly formed compact and cancellous bone. In addition to dose level, incorporation of strontium into bone also depends on length of exposure. Strontium content in rat femur doubled from 10 to 25 days during strontium exposure. In animal studies, strontium incorporation in bone reached a plateau, which was lower in females than in males. This observation may be due to differences in gastrointestinal uptake between males and females. However, there has been no evidence of gender difference in humans [4].

Strontium is removed from bone by a combination of mechanisms: clearance resulting from exchangeable pools of bone; long-term exchange processes in which strontium in the apatite crystal is displaced presumably by calcium; and removal from mineral phase and the matrix by osteoclastic resorption [4]. After a single intravenous injection in two adult males, the estimated elimination half-life of strontium was calculated to be 50 days. Other experiments suggest that the terminal half-life may be 3 years for humans, and may be negatively affected by clodronate or enhanced by vitamin D₃ [4].

Strontium overload and bone disease

Animal studies

Several studies have shown strontium to be associated with osteomalacia. Studies in normal rats demonstrated that high doses of strontium, > 8 mmol/kg/day, induced alterations of mineralization expressed by a decreased bone mineral density and decreased size of bone apatite [13]. In studies of ovariectomized rats, strontium renelate acted as an uncoupling agent that diminished bone resorption while maintaining bone formation [14]. In rats with chronic renal failure, SrCl₂ concentrations of 10 g/l induced mineralization defects, with bone strontium content 160-fold higher than in the bone of control rats [15].

The accumulation of metals in bone may be synergistic. Aluminium bone content was higher in animals receiving both aluminium and strontium compared with those receiving only aluminium. Histomorphometric studies showed a greater decrease in the bone formation rate of animals treated with both strontium and aluminium compared with those treated with strontium alone. Bone formation rate was decreased, and there was a decrease in the double-labelled bone surface and a decrease in mineral

apposition rate; these observations indicated a mineralization defect in the bone of those animals. However, some rats with normal apposition rates could be observed in this study [15].

Osteomalacia and dialysis patients

Bone biopsies in dialysis patients demonstrated an association between increased bone strontium levels and the presence of osteomalacia. Histological examination and determination of strontium content and strontium/calcium ratios were performed on 100 biopsies of ESRD patients from dialysis centres throughout the world. The results demonstrated that strontium concentration and strontium/calcium ratios in osteomalacic bone were significantly increased when compared with the other types of renal osteodystrophy. The strontium concentration of dialysis patients was elevated in osteomalacic bone ($91 \pm 51 \mu\text{g/g}$) compared with hyperparathyroid bone disease ($48 \pm 32 \mu\text{g/g}$), adynamic bone disease ($48 \pm 25 \mu\text{g/g}$), mixed bone disease ($45 \pm 42 \mu\text{g/g}$) and normal histology ($30 \pm 24 \mu\text{g/g}$). Furthermore, bone strontium levels were significantly correlated with bone aluminium levels in the bone of osteomalacia patients. The results of the study do not distinguish whether the osteomalacia was the result of a single metal, or synergy between both metals [16].

Strontium contamination in dialysis fluids

Strontium contamination has been found in the final dialysate of dialysis centres in developing countries. Strontium levels were measured throughout the process of purification and preparation for dialysis. Although strontium levels were decreased during purification, there was increased ordering in some centres after osmosis. After water exited the dialysis machine, some dialysis centres had high strontium levels compared with others in which there was no strontium increase. Serum strontium levels were correlated to strontium content in the dialysis fluids, with the highest serum strontium levels found in patients of dialysis centres in Brazil, Costa Rica and Paraguay. It was determined that strontium levels were increased in those dialysis centres using acetate-based concentrates, as opposed to those using bicarbonate-based concentrates, in which strontium levels did not increase. Thus, the use of acetate-based concentrates may be a source of further strontium intoxication. In addition to contaminated dialysis concentrates, other factors played a substantial role in the accumulation of strontium; these included the serum calcium concentration, the use of vitamin D supplements and the consumption of seafood [3].

A recent study documents osteomalacia in bone biopsies

We recently studied 271 bone biopsies taken from patients of French dialysis centres from 1988 to 1996. This period was chosen because aluminium intoxication

had begun to diminish following the removal of aluminium-containing phosphate binders, beginning in 1988. Of the 271 bone biopsies, nine (3.3%) revealed osteomalacia, which we compared with 23 biopsies with hyperparathyroid bone disease and 24 with adynamic bone disease. Control values were determined from bone biopsies of normal patients enrolled in studies for osteoporosis. Histomorphometric static and dynamic indices did not show a correlation between bone formation and bone strontium content (Table 1). Cellular activity represented by osteoblast surfaces and the number of osteoclast cells was comparable between osteomalacia and normal patients. Bone strontium was 1.5-fold higher in patients with osteomalacia ($0.030 \pm 0.005\%$) than in controls ($0.019 \pm 0.002\%$) or in the other types of renal osteodystrophy [17].

Stainable aluminium surfaces were low in the bone of osteomalacia and hyperparathyroidism patients, and slightly elevated in patients with adynamic bone disease. The level of double-labelled surfaces for all nine osteomalacia patients was zero. However, no real differences in single-labelled surfaces existed between osteomalacia, adynamic bone disease and osteitis fibrosa, indicating that mineralization was not fully impaired. Strontium content was increased in bone

Table 1. Histomorphometric data according to the bone disease

Parameter	Osteomalacia ($n=9$)	Normal values
Ob.S/BS (%)	7.1 ± 2.2	5.4 ± 1.9
Oc.S/BS (%)	0.6 ± 0.21	1.69 ± 0.73
N.Oc/T.Ar (mm^2)	0.58 ± 0.16	0.79 ± 0.37
MAR ($\mu\text{m/day}$)	0	0.63 ± 0.17
sLS/BS (%)	18.2 ± 4.4	–
dLS/BS (%)	0	13.2 ± 1.2
MS/BS (%)	18.2 ± 4.4	14.2 ± 1.3
BFR ($\mu\text{m/day}$)	0	0.089 ± 0.022
Al.S/BS (%)	20.5 ± 9.6	0
Strontium content (% mol/mol)	0.030 ± 0.005	0.019 ± 0.002

Adapted from [17].

The following trabecular parameters were measured and expressed according to the standardized nomenclature: Ob.S/BS, osteoblast surface as percentage of bone surface covered with osteoblast, trabecular bone surface referent; Oc.S/BS, osteoclast surface as percentage of bone surface covered with osteoclast, trabecular bone surface referent; N.Oc/T.Ar, osteoclast number expressed per mm^2 of tissue sections.

Aluminium was measured on undecalcified sections using AluminonTM staining, and was expressed as Al.S/BS (percentage of aluminium surface covered with aluminium, trabecular bone surface referent).

The dynamic parameters of trabecular bone were: sLS/BS, single-labelled surface as percentage of trabecular surface covered with one single label, trabecular bone surface referent; dLS/BS, double-labelled surface as percentage of trabecular surface covered with double label, trabecular bone surface referent; MS/BS, total length of labelled surfaces (sLS/BS + dLS/BS); MAR, mineral apposition rate expressed in $\mu\text{m/day}$; BFR, bone formation rate calculated as (sLS/BS + dLS/BS) \times MAR, expressed as $\mu\text{m/day}$.

Normal values of indices of bone formation [26] and bone resorption [27] are those of normal subjects without bone disease.

of osteomalacia patients compared with the other bone diseases and the controls. Although the observation involved only nine patients, the increase was statistically significant [17].

Clinical implications and relationship to other metals

The evolution of treatment regimens in renal failure has led to a corresponding change in the prevalence of different types of renal osteodystrophy [17]. Whereas aluminium-related bone disease has declined, osteomalacia still persists at a low prevalence [10]. As early as the 1970s, studies have demonstrated the accumulation of metals in the bone of renal failure patients [18]. This accumulation of metals is not unexpected, since elements such as strontium are excreted mainly by the kidney [1]. Several metals, such as chromium, zinc, tin and strontium, were shown to accumulate in the bone of dialysis patients [8]. Furthermore, increased strontium concentrations and strontium/calcium ratios have been observed in the bone of osteomalacia patients compared with other renal osteodystrophies [19].

Studies show that strontium is incorporated and retained in newly formed mineralized bone according to dose, exposure, gender and age [1]. High doses of strontium induced mineralization defects in normal rats [13,14], while rats with chronic renal failure developed osteomalacia at high doses of strontium [15]. Rats loaded with aluminium developed adynamic bone disease, whereas rats receiving both strontium and aluminium developed adynamic bone disease or a more severe form of osteomalacia. The increased severity of mineralization defects resulting from loading by both aluminium and strontium indicates a possible synergy between the elements in the development of osteomalacia. This finding becomes more striking when considered with epidemiological studies in bone biopsies in which aluminium and strontium content was elevated for osteomalacia compared with other bone diseases. Aluminium and strontium content is higher in patients with osteomalacia. However, these concentrations correlated with each other, suggesting that mineralization defects may be the result of several metals.

The observation that increased bone strontium levels were associated with osteomalacia in bone biopsies, and not with adynamic bone disease, indirectly indicates that strontium accumulation did not occur secondarily to the low turnover state in osteomalacia.

In developing countries, the use of contaminated dialysis concentrates was responsible for elevated strontium levels in dialysis fluids. Levels were elevated in dialysis fluids prepared from acetate-based concentrates, as opposed to bicarbonate-based concentrates. Epidemiological studies show that patients at dialysis centres with high strontium levels in dialysis fluids are at risk of high serum levels of strontium and of developing osteomalacia [16].

In a region of Turkey where there were high concentrations of strontium in the soil, and where the nutrition was based mainly on cereals, a high prevalence of a rickets-like disease was observed in children with normal renal function compared with children living in regions with low soil strontium [20]. It is interesting to note that animals with normal renal function administered strontium displayed bone lesions with histological resemblance to those seen in vitamin D-deficient rickets. However, strontium-induced rickets did not respond to vitamin D supplementation [3].

Conclusions

In our recent study of bone biopsies, aluminium levels in osteomalacia patients were below the toxicity threshold for aluminium. However, the observed defects in bone mineralization may have resulted from the presence of other metals or trace elements in the protein matrix, or synergy between the metals. In addition, our study reported total aluminium content, whereas it was noted previously that stainable aluminium at the mineralization front is more sensitive than total bone aluminium in identifying toxicity [11,21]. Another explanation for the increased strontium bone content might be that patients with osteomalacia received higher doses of vitamin D, as calcitriol may increase strontium absorption. While most patients in this study received vitamin D derivatives, specific data to evaluate this hypothesis are not available.

It is difficult to explain the accumulation of osteoid without bone formation. One explanation suggests that the osteoprogenitor cycle becomes disturbed, accompanied by damaged osteoblast cells that eventually become dysfunctional because of an event prior to strontium overload. Perhaps the osteoblast cells are still capable of forming osteoid, but are unable to mineralize, and eventually become non-functional. Moreover, the osteomalacia may be merely an endpoint of a dynamic pathology in which the causative agent is no longer present with the histological finding.

The experience of the last three decades has shown that the evolution of dialysis treatment has caused changes in the prevalence of different forms of renal osteodystrophy. The exposure of dialysis patients to biologically active metals through medications has proved disastrous in the past and should serve as a caution in the use of other metal-containing compounds. Prolonged administration of metals to dialysis patients, such as the proposed use of lanthanum in phosphate binders, should be evaluated carefully for absorption and long-term toxicities. Interactions between lanthanum and other accumulated metals, as well as interactions with other compounds of the uraemic syndrome, should be investigated for altered uptake, increased half-life, synergism or altered metabolism leading to increased toxicity.

Although data from several studies point to a causative role for strontium in the development of osteomalacia, more studies are necessary to demonstrate a pathological relationship conclusively. Studies are also needed to understand the ramifications of chronic exposure to strontium at lower doses. While studies in normal rats have shown that strontium does not exert toxic effects on bone mineralization when given at doses <1% in the diet—for both long- and short-term exposure—little is known about these effects in rats with renal insufficiency or in uraemic patients [22–25].

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