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Incorporation and Distribution of Strontium in Bone

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The distribution and incorporation of strontium into bone has been examined in rats, monkeys, and humans after oral administration of strontium (either strontium chloride or strontium ranelate). After repeated administration for a sufficient period of time (at least 4 weeks in rats), strontium incorporation into bone reaches a plateau level. This plateau appears to be lower in females than in males due to a difference in the absorption process. Steady-state plasma strontium levels are reached more rapidly than in bones, and within 10 days in the rat. The strontium levels in bone vary according to the anatomical site. However, strontium levels at different skeletal sites are strongly correlated, and the strontium content of the lumbar vertebra may be estimated from iliac crest bone biopsies in monkeys. The strontium levels in bone also vary according to the bone structure and higher amounts of strontium are found in cancellous bone than in cortical bone. Furthermore, at the crystal level, higher concentrations of strontium are observed in newly formed bone than in old bone. After withdrawal of treatment, the bone strontium content rapidly decreases in monkeys. The relatively high clearance rate of strontium from bone can be explained by the mechanisms of its incorporation. Strontium is mainly incorporated by exchange onto the crystal surface. In new bone, only a few strontium atoms may be incorporated into the crystal by ionic substitution of calcium. After treatment withdrawal, strontium exchanged onto the crystal is rapidly eliminated, which leads to a rapid decrease in total bone strontium levels. In summary, incorporation of strontium into bone, mainly by exchange onto the crystal surface, is dependent on the duration of treatment, dose, gender, and skeletal site. Nevertheless, bone strontium content is highly correlated with plasma strontium levels and, in bone, between the different skeletal sites. (Bone 28: 446–453; 2001)

Key Words: Strontium; Bone formation; Mineralization; Osteoporosis; Gender difference; Elimination rate.

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Introduction

The prevalence of osteoporosis, characterized by low bone mass, enhanced bone fragility, and fracture risk, is increased in postmenopausal women. This may be due to estrogen deficiency, causing an imbalance between bone resorption and formation,[56] and possibly also to impaired intestinal absorption of calcium. The risk of developing osteoporosis is also increased by prolonged corticosteroid treatment, especially in children, and in patients with rheumatoid arthritis, hypogonadism, or malabsorption.[10,19] Current therapy for osteoporosis includes dietary supplementation of calcium and vitamin D, in addition to treatment with estrogen, calcitonin, bisphosphonates, selective estrogen-receptor modulators (SERMs), or fluoride.[14,67] Estrogen, bisphosphonates, SERMs, and calcitonin reduce bone resorption, whereas fluoride stimulates bone formation. In addition to these, several other treatment strategies are currently being developed,[14,61] including strontium ranelate (S12911), a potential new antiosteoporotic drug composed of two atoms of stable strontium (Sr^{2+}) and an organic part (ranelic acid).

This article reviews studies reported in literature and in reports from the Institut de Recherches Internationales Servier (Courbevoie, France), concerning the metabolism and effects of strontium after intake of trace amounts of strontium isotopes, high doses of stable strontium, and potential therapeutic doses of strontium ranelate (S12911). In order to facilitate comparison of doses between different studies, all doses are expressed as Sr^{2+} equivalent quantities.

A beneficial effect of low doses of stable strontium in the treatment of osteoporosis was reported almost half a century ago.[69] However, as suggested by Skoryna,[70] the therapeutic potential of such agents may since have been neglected, due to a confusion of normal, stable Sr^{2+} (^{84}Sr, ^{86}Sr, ^{87}Sr, and ^{88}Sr) with its radioactive isotopes (^{85}Sr, ^{87}mSr, ^{89}Sr, and ^{90}Sr).[16] Strontium and calcium both belong to the alkaline earth elements, and resemble each other in that >99% of the total amount in the body is localized in bone. This article investigates the effects of strontium on bone, the main factors influencing the incorporation and distribution of strontium in bone, and how such information may be used in the prevention and treatment of osteoporosis. In clinical practice, only a limited number of bone samples may be collected, and generally only from the iliac crest. Experimental data, obtained from studies with rats and monkeys, have enabled the establishment of certain general rules that may prove to be

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useful in clinical practice to estimate the bone strontium content at a determined skeletal site. This could further be used to adjust the dual X-ray absorptiometry (DXA) measurements, because strontium induces an overestimation of bone mineral content (BMC) and bone mineral density (BMD). It has recently been shown that this overestimation is linearly linked to the bone strontium content, and that the adjustment factor to be used for in vivo measurements in humans is 10% for a Sr/(Sr + Ca) (mol%) in bone within the range of 0%–3.5 mol%.[57]

Effects of Strontium on Bone

Strontium has a beneficial effect on bone. In vitro studies have shown that strontium enhances the replication of preosteoblastic cells, and stimulates bone formation in cell and calvarial cultures in vitro.[12] Furthermore, it has been demonstrated that strontium ranelate decreases bone resorption in vitro.[73] These effects, observed either on isolated cells or on tissue culture, have also been found in vivo. Treatment with low doses of strontium (316–634 mg/kg per day Sr^{2+}), administered as strontium chloride or strontium ranelate for 9–26 weeks, stimulates bone formation and decreases bone resorption in rodents and humans, resulting in increased cancellous bone volume, while mineralization remains normal.[21,25,38,39,40,45,73] Treatment of adult rats or mice for 8 weeks with low oral doses of strontium (167.8 mg/kg per day in rats and 540 mg/kg per day in mice), fluoride (0.99 mg/kg per day in rats and 0.8 mg/kg per day in mice), or both combined resulted in Sr^{2+}/Ca^{2+} ratios of about 5% in serum and in the femur, an increased number of bone-forming sites, and increased vertebral bone volume.[24,40] The treatment with strontium was associated with increased osteoid and osteoblast surfaces, showing that the number of bone-forming sites had been increased. The strontium-induced increase of bone formation results in a better mechanical resistance of bones. This was observed in a study of long-term (2 year) treatment with strontium ranelate in the rat, which showed increased bone mass and increased bone strength of the vertebrae in males[4] and midshaft humerus in females.[3] The increase in bone strength was significantly correlated with the increase in BMD. These effects, increase of bone formation and decrease of bone resorption, were also found in ovariectomized Sprague-Dawley and Wistar rats.[41,51] No effect on growth or body weight in any of the short- or long-term studies in the rat, and no detectable adverse effects on the mineral profile, bone mineral chemistry, or bone matrix mineralization were observed. Furthermore, the strontium-induced increase in osteogenesis was not associated with changes in circulating levels of $1,25(OH)_2$ vitamin D or in parathyroid hormone effects.

Taken together, these results indicate that, in vitro, strontium increases the number of osteoblasts and decreases the number and the activity of osteoclasts,[12,73] and that, in the normal or ovariectomized rat, strontium ranelate acts as an uncoupling agent that diminishes bone resorption while maintaining bone formation.[37,41]

In humans, a significant and clinically relevant increase in the lumbar spine BMD of postmenopausal osteoporotic white women was observed after 12 months of treatment with strontium ranelate at 2.0 g/day (517 mg Sr^{2+}/day).[50] After 2 years, a 2.9% annual increase in lumbar BMD, adjusted for strontium content, was observed at this dose.[49] Reginster[61] reported that prolonged administration of strontium ranelate to postmenopausal osteoporotic women resulted in a decoupling between bone resorption and formation, yielding a significant increase in the lumbar spine BMD of treated subjects.

The detailed cellular mechanisms underlying the beneficial effects of low strontium doses on bone formation are not completely known. However, Quarles raised the hypothesis that a calcium-sensing mechanism could be implicated in the strontium effects.[58] The addition of Sr^{2+} to parathyroid cells induces rapid and sustained increases in intracellular Ca^{2+} and 1,4,5-inositol-triphosphate, presumably by interaction with parathyroid cell membrane Ca^{2+} receptors.[68] There is evidence that calcium released from bone may regulate the function of bone cells via cation-sensing mechanisms in osteoblasts and osteoclasts.[58] This mechanism implies the previously identified calcium-sensing receptor,[11] because the calcium-sensing receptor has been identified in osteoblasts from mouse, rat, and bovine bone.[13]

All of the aforementioned data indicate that a therapeutic effect of treatment with controlled doses of strontium ranelate is obtained by a dual mechanism of action: inhibition of bone resorption and augmentation of bone formation.

Uptake and Deposition of Strontium in Bone Matrix

Bone mineral consists mainly of a poorly crystalline fraction made of apatite and other crystalline calcium phosphate complexes.[22] Strontium has a great affinity for bone[33] and is incorporated into it by two mechanisms: surface exchange or ionic substitution. However, in treated animals, even with large doses over a long period of time, the total amount of strontium in bone is always very low as compared with calcium (only a few percent of the bone calcium content), because a theoretical maximum of one calcium atom out of ten can be substituted by a strontium.[9]

Important contributions to the understanding of the uptake and exchange of trace elements in bone have been made by Marshall,[42] Marshall et al.,[43] Newton et al.,[53] and Rowland,[65,66] and discussed by O'Flaherty.[55] They have identified that three essential mechanisms determine the uptake and release of bone-seeking elements:

- Apposition, leading to an increase in mineral volume, which is the main feature of bone metabolism in neonatal and young mammals.
- Resorption, which, together with apposition, contributes to the modeling of the growing skeleton. In adulthood, a continuing low-level resorption/apposition remodeling process maintains healthy bone and restructures the bone in response to changing functional demands.
- Surface exchange and diffuse exchange. Rapid exchange between blood and bone calcium, or similar trace elements, takes place at all bone surfaces in contact with blood. It has been estimated that the exchangeable pool contains 0.65% of the total bone calcium in the human skeleton.[66] Diffuse exchange is a slow process by which bone-seeking elements can penetrate the entire bone volume. In humans, slow exchange of trace elements with bone Ca^{2+} is considered to be the dominant mechanism of trace element uptake during adulthood.[55]

MacDonald et al.[34] observed a rapid decrease in the Ca^{2+}/Sr^{2+} ratio in rat and mouse femur during the first day of oral administration of $SrCl_2$ in drinking water, followed by a much slower decrease in Ca^{2+}/Sr^{2+} ratios during 6–8 weeks. The investigators postulated that Sr^{2+} is taken up into bone by two different mechanisms: (1) an initial rapid mode, depending on osteoblastic activity, which is eventually saturated, and whereby Sr^{2+} is taken up by ionic exchange with bone Ca^{2+}, binding of Sr^{2+} to preosteoid proteins, or combinations of these; and (2) a second slower mechanism involving the incorporation of Sr^{2+} into the crystal lattice of the bone mineral. The concept of two different phases involved in the uptake of strontium into bone has since been generally accepted — that is, a relatively rapid uptake into new bone and long-term exchange processes in old bone.[60] X-ray crystallographic experiments have demonstrated that incorpora-

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Table 1. Crystal lattice parameters of apatite from iliac crest of male cynomolgus monkeys after 13 weeks of treatment with oral strontium ranelate doses ranging from 100 to 750 mg/kg per day (Sr^{2+} dose: 34–255 mg/kg per day)[9]

	Axis length ± SD (Å)	
Cell axis	Treated animals (all doses combined, n = 12)	Control group (n = 4)
a	9.368 ± 0.057	9.375 ± 0.027
c	6.900 ± 0.011	6.878 ± 0.010

a and *c* are reticular parameters of the crystal.

tion of strontium into the bone of cynomolgus monkeys treated with oral strontium ranelate for 13 weeks took place mainly by ionic exchange at crystal surfaces, and to a minor extent by heteroionic substitution (with a maximum of one calcium atom out of ten being substituted) into the crystal lattice.[9] The differences in strontium incorporation into bones were further analyzed at a microscopic level using the X-ray microanalysis technique, and the influence of the presence of strontium on the size of the crystal was studied by X-ray powder diffraction and Raman microspectrometric techniques. These techniques were applied on bone mineral samples obtained from the iliac crest of male cynomolgus monkeys treated for 13 weeks with oral doses of strontium ranelate. The doses ranged from 100 to 750 mg/kg per day of strontium ranelate, corresponding to 34–255 mg/kg per day of Sr^{2+}.[9] The X-ray microanalysis method provided a semiquantitative evaluation of the amount of strontium taken up by the bone mineral substance, and its localization. Combined with X-ray diffraction and secondary Raman spectroscopic images, it was demonstrated that strontium was dose-dependently taken up by the bone mineral and heterogeneously distributed in compact and cancellous bone, with a higher amount in newly formed bone tissue than in old bone tissue. The strontium was heterogeneously distributed, with a three- to fourfold higher strontium content in new than in old compact bone, and approximately 2.5-fold higher strontium content in new than in old cancellous bone. At all the applied doses, incorporation of strontium produced no significant change in the crystal lattice parameters, even if the ionic radius of Sr^{2+} (1.13 Å) is slightly larger than that of Ca^{2+} (0.99 Å) (**Table 1**). Neither were there changes of the cohesion properties of the mineral crystals, which exhibited properties of "young" bone (i.e., low intracrystal distances[9]). Even at the highest dose of 255 mg Sr^{2+}/kg per day, the apatite crystals in the treated animals were intermediates between a "physiologic" calcium hydroxyapatite and an apatite where one calcium atom out of ten was substituted by a strontium atom. In vitro chemical experiments have also shown that Ca^{2+} may be exchanged by Sr^{2+} in synthetic calcium hydroxyapatite.[15] Furthermore, there was a good correlation between the bone strontium content obtained by X-ray microanalysis and by chemical determination carried out by atomic emission spectrometry (after bone calcination) on the same bone samples.[9,20,26]

As reviewed by Comar and Wasserman,[16] it emerged early on as a general pattern that, when there was a metabolically controlled passage of ions across a biological membrane in the living organism, calcium was transported more efficiently than strontium. Others have shown that the radioisotopes ^{45}Ca and ^{85}Sr are both incorporated into cultured live embryonic chick calvariae in vitro at 37°C by an uptake mechanism that favors ^{45}Ca over ^{85}Sr.[76] Slices of various soft tissues from the rat also showed higher uptake of ^{45}Ca than of ^{85}Sr in vitro, but the discrimination in favor of ^{45}Ca was much less pronounced in bone than in soft tissues.[30,31] Similar $^{89}Sr/^{45}Ca$ ratios in bone were reported by

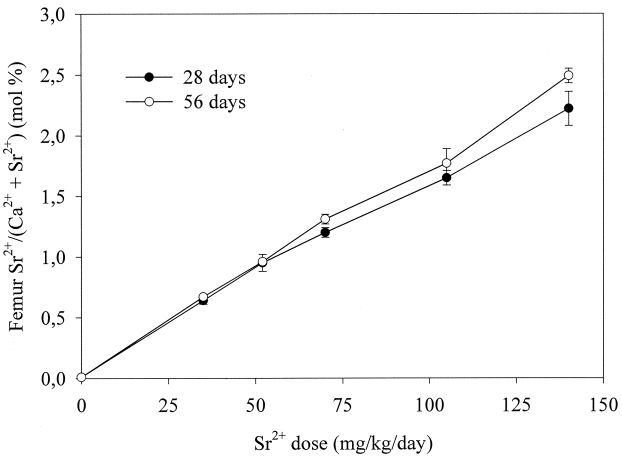

Figure 1. Strontium content in femoral diaphysis of male Wistar rats after 28 and 56 days of oral treatment with strontium ranelate (mean ± SEM). Data from Meunier.[48]

others after repeated intraperitoneal injections in the rat.[33] As discussed by Nijweide,[54] apparent discrepancies between results concerning strontium vs. calcium discrimination from in vivo and in vitro studies (in which synthetic apatite crystals have been used) may have been due to: (1) differences in transport of strontium and calcium from blood into bones; (2) differences between the composition of the interstitial fluid in bone tissue and the solution used in in vitro experiments; and (3) a higher degree of plasma protein binding of calcium than of strontium. The discrimination of biological membranes in favor of calcium over strontium has been clearly demonstrated in the kidneys and in the gut, whereas it is less clear to what extent such discrimination may occur in the transport into bone from the blood stream.

Factors Influencing Incorporation of Strontium Into Bone

Animal studies have identified five different factors influencing the incorporation of strontium into bone: dose; plasma strontium level; gender; duration of treatment; and skeletal site.

Dose

Experimental data have clearly demonstrated that the strontium content in bone increases with the administered dose.[48] As shown in **Figure 1**, the bone strontium content in rat femur was proportional to the administered dose after 4 weeks and 8 weeks of treatment with strontium ranelate at doses corresponding to 35–140 mg Sr^{2+}/kg per day. However, at higher dose levels, the strontium content in bone tends to reach a plateau level.[36] Already after 10 days of treatment, the strontium content of rat femur showed a dose-dependent increase up to 255 mg Sr^{2+}/kg per day, but the relative increase was less from 93.5 to 255 mg Sr^{2+}/kg per day than from 0 to 93.5 mg Sr^{2+}/kg per day.[36] The most likely explanation for the plateau effect and the lack of proportionality between dose and bone level seems to be a saturation of the gastrointestinal absorption mechanisms.[32] As bone strontium content is parallel to plasma strontium concentration, neither of these are proportional to the dose (see below).

Plasma Strontium Level

Within 4 weeks of oral dosing, the plasma Sr^{2+} concentration in rats and monkeys tends to reach a plateau level, which is

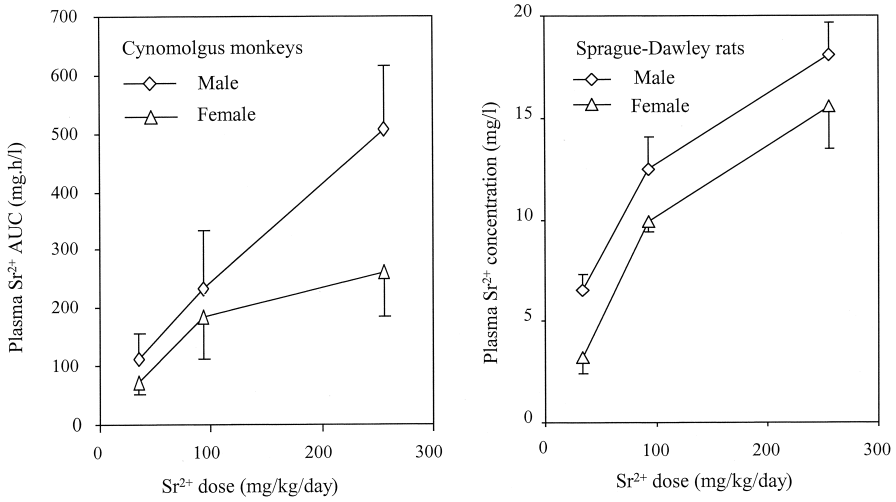

Figure 2. Plasma strontium concentrations in cynomolgus monkeys and Sprague-Dawley rats after 26 weeks of oral treatment with strontium ranelate doses corresponding to 34, 93.5, and 255 mg Sr^{2+}/kg per day (mean ± SEM). Data from Rousselet.[63,64]

related to the administered dose.[63,64] However, like the bone strontium content,[36] the plasma levels showed a relatively smaller increase from 93.5 to 255 mg Sr^{2+}/kg per day than at lower doses, both in rats and monkeys (**Figure 2**). This is likely due to saturation of strontium absorption from the gastrointestinal tract at higher doses.

Absorption of strontium from the gastrointestinal tract of the rat takes place by a process that discriminates against dietary strontium in favor of calcium.[17] Pharmacokinetic experiments with human volunteers have indicated that gastrointestinal absorption of strontium takes place, at least partly, by an active transport mechanism involving a calcium-binding protein.[32] It is of interest to note, therefore, that although the plasma strontium levels showed a nonlinear relationship with the administered dose, there was a direct linear correlation between plasma concentration and incorporation of Sr^{2+} into the iliac crest of cynomolgus monkeys after 26 weeks of oral treatment, within the applied dose range of 34–255 mg Sr^{2+}/kg per day (**Figure 3**).[2,63,64]

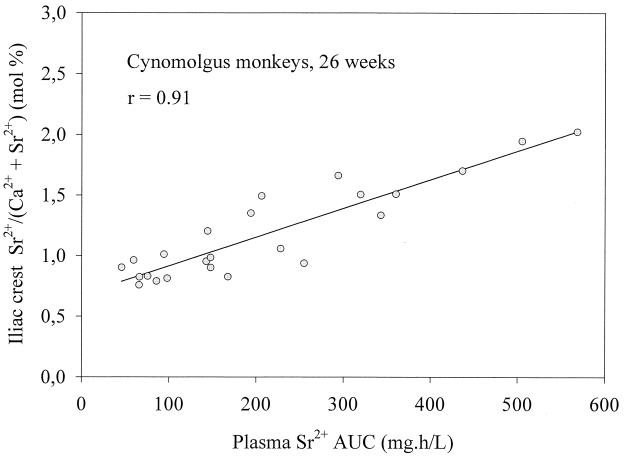

Figure 3. Relationship between strontium concentrations in the iliac crest and in plasma from male and female cynomolgus monkeys after 26 weeks of oral treatment with strontium ranelate doses corresponding to 34, 93.5, and 255 mg Sr^{2+}/kg per day. Data from Allain[2] and Rousselet.[63,64]

Gender

The analysis of trace levels of strontium in rats fed a normal laboratory chow (1% Ca and 0.02% Sr) showed no gender differences in strontium concentrations in the femur or in plasma.[74] However, by oral administration of strontium ranelate, female rats obtained lower bone strontium contents than their male counterparts, but this difference was less pronounced in monkeys.[1,62]

Apparently, the higher strontium concentrations in male rats are due to differences in the gastrointestinal absorption of strontium between males and females. As shown in Figure 2, after 26 weeks of oral treatment, the plasma strontium levels were also higher in male Sprague-Dawley rats than in females, whereas, in cynomolgus monkeys, a similar gender difference was observed at 255 mg Sr^{2+}/kg per day, but not at lower doses. So far, there has been no evidence of a similar gender difference in humans.

Duration of Treatment

Besides the dose level and gender, incorporation of strontium into bones also depends on the length of treatment.[36,48] Although the strontium content in rat femur doubled from 10 to 25 days of treatment with strontium ranelate,[36] there was only a slight increase from days 28–56, as shown in Figure 1. It seems that bone strontium content in the rat approaches a plateau level after approximately 4 weeks of treatment. However, the plasma strontium levels in rats were virtually identical after 10 and 29 days of treatment,[35] which demonstrates that a plateau plasma level had been reached within 10 days.

Skeletal Site

The incorporation of strontium into bone after oral strontium treatment depends upon the skeletal site. This is illustrated in **Figure 4**, which shows the strontium content in the femoral diaphysis, a lumbar vertebra, and in the iliac crest of monkeys after 26 weeks of treatment with three different doses.[2,63,64] The bone strontium content in the diaphysis of the femur was always lower than in the lumbar vertebra, which itself was always lower than in the iliac crest.

The main biological determinant of bone mineralization is the rate of turnover.[23] During rapid growth and periods of high remodeling, mineralization is shifted toward lower mineral den-

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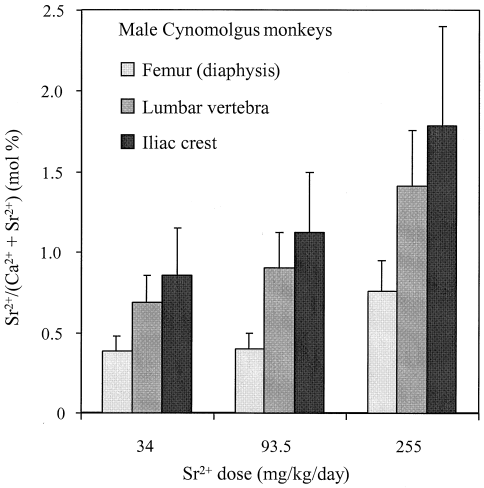

Figure 4. Strontium content in different skeletal sites after 26 weeks of oral treatment with strontium ranelate (mean ± SEM). Data from Allain[2] and Rousselet.[63,64]

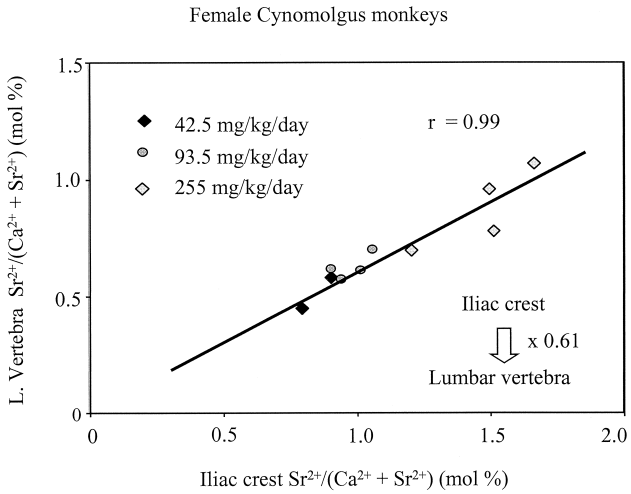

Figure 6. Relationship between strontium content in two different skeletal sites of female cynomolgus monkeys after 26 weeks of oral treatment with strontium ranelate. Data from Allain[2] and Rousselet.[63,64]

sity and, during aging and periods of low remodeling, mineralization is shifted toward higher mineral densities. The skeletal repartition of strontium is related to the relative cortical and cancellous proportions of the bone, because bone turnover is higher in cancellous than in cortical bone, and newly formed bone is more abundant in cancellous than in cortical bone.[9] This is demonstrated in **Figure 5**, which shows that the strontium content was higher in cancellous bone than in cortical bone of cynomolgus monkeys, treated for 13 weeks with various strontium doses.

Kshirsagar et al.,[31] using 7-month-old rabbits, found that strontium uptake, and discrimination against strontium in favor of calcium, varied between the different bones of the body. Kirkeby and Berg-Larsen[28] examined the regional distribution of blood flow in the rat hind limb by injection of radioactively (^{141}Ce)-labeled microspheres, and found a close association between blood flow and mineral turnover in rat skeletal tissue, determined by the rate of ^{85}Sr incorporation. Skeletal blood flow in 20 untreated patients with idiopathic or postmenopausal osteoporosis, measured by ^{18}F techniques, correlated with an index of ^{85}Sr uptake into the exchangeable pool of bone.[59] This suggests that variations in the uptake of strontium between various skeletal sites may depend, at least partially, on regional blood flow.

The bone strontium content in female cynomolgus monkeys treated for 26 weeks was lower in the lumbar vertebra than in the iliac crest.[2,63,64] This may be due to a higher turnover, and a higher regional blood flow, in the iliac crest than in the lumbar vertebra. However, as shown in **Figure 6**, the strontium levels in the iliac crest and lumbar vertebra were correlated, independently of the dose ($r = 0.99$; slope = 0.61),[2,63,64] which suggests that the strontium content of the lumbar vertebra might be estimated using the strontium content of the iliac crest, and an adjustment factor of 0.61.

Uptake and Elimination of Strontium From the Organism

The body handles strontium in a similar way to calcium in that it is absorbed from the gut, concentrated in bone, and excreted mainly in the urine. However, the mammalian kidney excretes strontium more rapidly than calcium.[18,46,72] Both elements are reabsorbed by the renal tubulus, and a higher rate of tubular reabsorption of calcium than of strontium is thought to be the major cause of this renal discrimination.[16,17]

The absorption of strontium and calcium from the gastrointestinal tract is carried out by the same mechanisms. It has long been suggested that excessive doses of strontium could disturb the calcium metabolism.[16] To assess the toxic dose levels, rats received daily strontium doses ranging from 87.5 to 875 μmol (i.e., 77–770 mg/kg per day Sr^{2+}) for 1 month.[52] Net intestinal

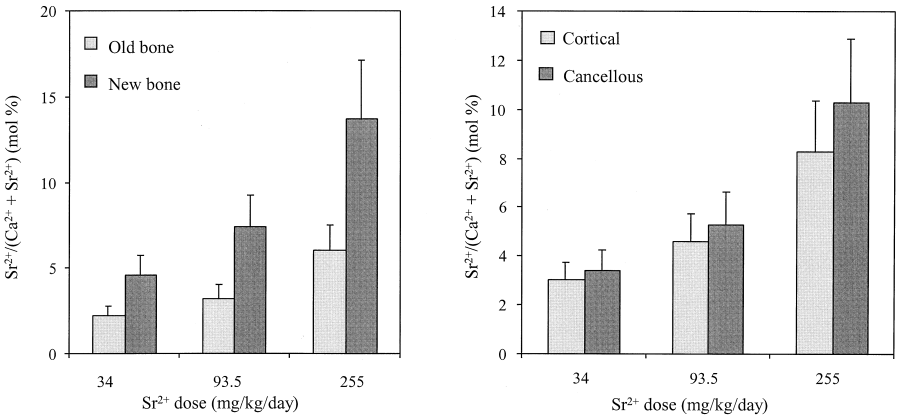

Figure 5. Influence of bone turnover on strontium incorporation in male cynomolgus monkeys (mean ± SEM) after 13 weeks of oral treatment with strontium ranelate, as determined by X-ray microanalysis techniques. Data from Boivin et al.[9]

calcium absorption, fractional calcium absorption (relative to intake) and calcium retention in the body were all markedly reduced in the group that received 875 μmol/day, but none of these parameters were significantly affected in the groups receiving less than 175 μmol/day (equivalent to 153 mg/kg per day Sr^{2+}).

Mechanisms discriminating uptake of strontium in favor of calcium develop gradually during maturation in rats, and it has been proposed that the high efficiency of strontium absorption by the small intestine early in life may be due to a deficiency in such absorptive discrimination.[74] Measurements of the relative renal clearances of calcium and strontium in young rats have confirmed that there is a discrimination of strontium in favor of calcium during tubular reabsorption, by a mechanism that is not fully developed in young rats before weaning.[75]

The clearances of the radionuclide ^{89}Sr ranged from 1.2 to 15.0 L/day (total clearance) and 0.1 to 11.5 L/day (renal clearance) in 26 patients undergoing radionuclide therapy.[7] The renal component accounted for 96% of the variance in total strontium plasma clearance. Elimination half-lives of strontium in human volunteers were determined from plasma strontium concentrations after a single oral dose of 2.5 mmol $SrCl_2$, and ranged from 37 to 58 h.[32] This indicates that a steady-state level of plasma strontium concentrations should be reached after 1–2 weeks. This has been specified in another study showing that steady-state plasma strontium levels had been reached within 10 days of oral treatment with strontium ranelate in the rat.[35] The elimination half-life of ^{85}Sr from blood in two adult men was estimated to be 50 days after a single intravenous injection.[6,16]

Elimination of strontium from bone takes place by a combination of three different processes: clearance from exchangeable pools of bone, displacement of strontium, presumably by calcium, from sites within the apatite crystal by long-term exchange processes, and volume removal from the mineral phase and the matrix by osteoclastic resorption. Radioisotope tracer studies have demonstrated that a terminal elimination phase of strontium from deeper bone compartments, which does not follow first-order kinetics (and thus has no half-life), and is much slower than the elimination rates, may be estimated from plasma concentration measurements.[43,44,47] In one study, after a single injection of strontium in rabbits, the content of strontium in the skull was determined by X-ray fluorescence in situ techniques for up to 8 months.[71] The investigators reported that the retention of strontium could be represented by a three-exponential model with a terminal half-life of 200–300 days. Another study evaluated the bone strontium content of samples from cynomolgus monkeys, which were collected 6 weeks after the end of a 13 week treatment period with oral strontium doses ranging from 34 to 255 mg/kg per day of Sr^{2+} (100–750 mg/kg per day of strontium ranelate).[9] The bone strontium content decreased substantially during the treatment-free period, regardless of the previously administered dose. Six weeks after cessation of the treatment the decrease was approximately 50% (**Figure 7**). This indicates that the first rate of elimination of strontium in monkeys is rather rapid with an estimated duration of 41 days. It has been proposed that the significant bone clearance of strontium observed in monkeys 6 weeks after cessation of treatment may be due to a rapid decrease in the amount of strontium taken up onto the surface of the crystals, without a significant decrease in heteroionic substitutions.[9] Furthermore, after 6 weeks, the heterogeneous distribution of strontium persisted with 3–3.5 times more strontium in new than in old bone. The reason could be that, as mentioned earlier, the uptake of strontium in old bone is mainly due to adsorption and exchanges at the crystal surface, whereas strontium taken up by heteroionic substitution during remodeling is more firmly linked to bone mineral substance. This suggests

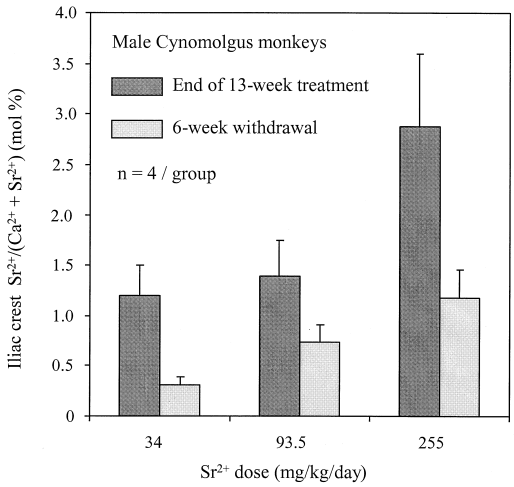

Figure 7. Bone strontium content at the end of a 13-week treatment period, and 6 weeks after withdrawal of treatment with strontium ranelate (mean ± SEM). Data from Allain[1] and Rousselet.[62]

that the terminal half-life of strontium is very long. This terminal half-life, estimated with a nonlinear model, seems to be of about 3 years for humans (J. F. Staub, personal communication), which is substantially more rapid than that of fluoride (elimination half-life of about 20 years)[5,8,77] and of biphosphonates (elimination half-life of about 10 years),[27] both of which are currently used for the treatment of osteoporosis.

The elimination of strontium from the organism may be affected by other agents. The effect of high-dose treatment with 24,25-dihydroxyvitamin D_3 [$24,25(OH)_2D_3$] or clodronate on bone resorption was assessed by Sr excretion in urine and feces.[29] Strontium-labeled rats were fed a low-Ca diet (0.08% Ca) and injected with $24,25(OH)_2D_3$ or clodronate for 14 consecutive days. Clodronate significantly decreased strontium output during both sampling weeks (i.e., decreased bone resorption), whereas treatment with $24,25(OH)_2D_3$ resulted in increased strontium output, indicating an increase in bone resorption.

Conclusions

The content of strontium in bone is determined by dose level and gender, both of which affect the plasma strontium levels. As illustrated in **Figure 8**, the incorporation of strontium into bone is directly related to plasma strontium levels, but it is also time-dependent, and reaches a plateau level after 3–4 weeks. Contrary to bone levels, plasma levels of strontium in rats reach a plateau level within 10 days of treatment.

Incorporation of strontium into bone is influenced by bone

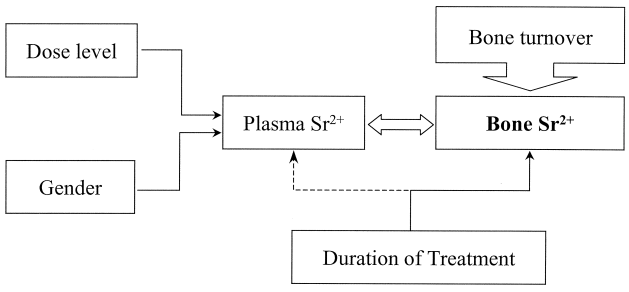

Figure 8. Factors influencing the incorporation of strontium into bones.

turnover. Therefore, cortical bone has a lower strontium content than cancellous bone after oral treatment with strontium ranelate.

Incorporation of strontium into bone takes place mainly by exchange at the crystal surface, and only a small amount of calcium in the apatite is substituted by strontium at pharmacological doses. This results in a rapid decrease in bone strontium levels after withdrawal of the treatment. The elimination of deeper incorporated strontium is much slower and depends on the remodeling activity of the bone.

A good correlation has been demonstrated between the strontium content in different skeletal sites. It should be possible, therefore, to estimate the bone strontium content of deep skeletal sites from experimental measurements of the strontium content in the iliac crest.

Once both the plasma and bone strontium contents have reached their plateau levels, there is a very good correlation between plasma and bone strontium levels. Therefore, plasma concentrations may be used to estimate the strontium content in bone after 4 weeks of treatment or longer, when adjustment factors relating plasma levels to bone contents have been experimentally determined. Such information would be highly useful in clinical practice for purposes of estimating bone strontium content from plasma concentrations, and would thus eliminate the need for the patient to undergo a bone biopsy.

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