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Review

# The biological role of strontium

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**Abstract**

This review summarises old and more recent literature on the biological role of the bone-seeking trace metal strontium (Sr). It covers areas of chemistry, nutrition, toxicity, transport across biological membranes, homeostasis, general physiology, calcium–strontium interactions, and particularly the role of strontium in bone. The promoting action of strontium on calcium uptake into bone at moderate strontium supplementation, and the rachitogenic action of strontium at higher dietary strontium levels are emphasised. The literature is summarised of the novel antiosteoporotic drug strontium ranelate, which appears to act by a combination of reduced bone resorption and increased uptake of calcium into bone.


*Keywords:* Strontium; Physiology; Bone; Medicine

## Introduction

Strontium (Sr) in human biology and pathology has attracted less attention than the other two important divalent metals calcium and magnesium, and over the years been an object of academic rather than clinical interest. Although this is still true, there is an increasing awareness of the biological role of Sr after the development of the drug strontium ranelate, which has recently been shown to reduce the incidence of fractures in osteoporotic patients [39,40,49]. Important contribution to the knowledge of Sr was obtained in the 1950s and 1960s. A comprehensive review on Sr was published 1964 [18]. The present updated review deals with normal functions of stable Sr, and covers areas of bone physiology in a broad sense inclusive of chemistry, toxicity, nutrition, intestinal absorption, renal excretion, homeostasis, and role in heart and muscle function. It summarises older and more recent publications relevant to medicine. Cellular and subcellular functions of Sr are not described in any detail.

## Chemistry

Sr was discovered in 1790 in a mine near the Scottish village Strontian and was isolated 1808. Sr is one of the alkaline earth metals. It never occurs free in nature, because metallic Sr oxidises easily forming strontium oxide, which has a yellowish colour. Sr is well known from the minerals celestite ($SrSO_4$) and strontianite ($SrCO_3$). Natural Sr is a mixture of four stable isotopes: $^{84}Sr$ (0.56%), $^{86}Sr$ (9.86%), $^{87}Sr$ (7.02%), and $^{88}Sr$ (82.56%). The elements of group 2 of the periodic system, to which Sr belongs along with Ca and Mg, form divalent cations in biological fluids, and have varying degrees of protein binding in biological fluids like serum or plasma. The protein binding of Sr in serum or plasma is in the same order of magnitude as that of Ca [64]. Some important differences among Mg, Ca, and Sr are listed in Table 1. It can be seen that Sr is a trace metal in the human body. Balance data for reference man can be thus summarised (mg Sr per day): intake by food and fluids 1.9; loss in urine 0.34; loss in feces 1.5; other losses, for example, in sweat 0.02, and hair $0.2 \times 10^{-3}$. Details of Sr quantities in organs and tissues have been compiled [53].

Radioactive Sr isotopes are dealt with only when they are used for physiological or diagnostic purposes. The characteristics of the radioactive Sr isotopes are summarised in Table 2. It can be seen that some of the Sr radioisotopes can be used in medicine. They have been used as excellent tools for kinetic studies, substituting for Ca in kinetic investigations because the two metals behave very much alike in the human body, both having strong bone-seeking properties. However, biological differences between the two elements exist, explicable in part by the larger size of the Sr molecule.

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Table 1
Physical properties of the biologically important elements of group 2 of the periodic system: magnesium, calcium, and strontium, and their distribution in the body of a 70-kg standard man

| Element | Atomic number | Atomic weight | Amount (g) | % of body mass |
|---|---|---|---|---|
| Mg | 12 | 24.32 | 19 | 0.027 |
| Ca | 20 | 40.08 | 1000 | 1.4 |
| Sr | 38 | 87.63 | 0.32 | 0.00044 |

Common transport paths for Ca and Sr have been described for many organs, Sr competing with Ca for intestinal absorption, renal tubular reabsorption, and so on. Accordingly, the use of Sr can create problems of evaluation, if radiostrontium is used as a marker of Ca kinetics. $^{90}$Sr has potentially deleterious consequences for the human body in case of exposure after nuclear accidents or use of atomic weapons due to its bone-seeking properties. The explanation hereof is twofold: (1) Radiostrontium damages capillaries and thereby compromises bone blood flow; (2) the affinity of Sr to chelating agents is no better than that of Ca, for example, if $CaNa_2EDTA$ is administered little Sr is chelated [29].

## Strontium sources

Sr comprises 0.02–0.03% of the earth's crust, from where the Sr of water derives. Sr is widely available. Its concentration in soil and drinking water varies between 0.001 and 39 mg/l, and in the United States, the concentration of Sr in drinking water is <1 mg/l [60]. A normal diet contains 2–4 mg Sr/day, most of it derived from vegetables and cereals. Thus, the amount of Sr in food of Western countries is negligible compared to Ca. The intake of Sr depends on the Sr contents of the diet, and for plants the concentration of Sr correlates with the Sr content of the soil, which is much lower than for Ca. According to earlier estimates, the overall relative abundance of Sr in the earth's crust is around 8 mg Sr/1000 mg Ca [27], but variations from one region to the other exist. Strontium is a plant growth stimulant and can replace calcium required by Chlorella [63]. Plants usually contain the same Sr/Ca ratio as their corresponding soil extracts, and this ratio varied in England between 1.4 and 5.7 mg Sr/1000 mg Ca. The higher values were found in extracts from two sandy, acid soils of low Ca content [7]. Early observations indicated that the Ca/Sr ratio in tissues and body fluids mirrored the Ca/Sr ratio in the diet [18].

## Strontium deficiency

Sr has never been shown to be an essential element, that is, causing death when absent, but Sr may in some plants promote growth [6]. Caries prevalence is inversely related to Sr levels in water, plaque, and enamel [21]. Administration of Sr in moderate doses prevented caries in rats [22]. The complicated issue of Sr and caries was reviewed 1983 [57].

Since Sr given as strontium ranelate augments bone Ca in experimental animals and reduces fracture rate in osteoporotic patients, it could be hypothesised that one feature of osteoporosis may be a certain degree of Sr deficiency, but data on bone Sr in normals are scarce. One investigation of trace elements in iliac crest biopsies of an experimental osteoporotic rabbit model did not show reduced bone Sr levels [66]. However, it has been shown that among the trace metals present in human bone, Sr was the only one that was correlated with bone compression strength [31].

## Strontium toxicity

Toxic symptoms due to overdosing of Sr have not been reported in man. However, intravenous administration of high doses of Sr induces hypocalcaemia due to increased renal excretion of Ca [41,52]. Farm animals have been studied intensively. Clearly, dietary Sr can vary widely without toxic symptoms appearing. Young pigs fed 6700 ppm Sr and 0.16% Ca suffered from incoordination and weakness followed by posterior paralysis [2]. Mature hens seem more resistant, egg weight and egg production being unaffected by a dietary Sr concentration of up to 30,000 ppm, but those variables were reduced at dietary concentrations of 50,000 ppm [25]. It was reported many years ago that high dietary Sr produced insoluble Sr phosphates leading to phosphorus deficiency [32] and to rickets, vide infra. The only stable Sr-containing chemical that is considered to be harmful to humans in small amounts is strontium chromate, the toxicity being caused by the chromium which is a genotoxic carcinogen [60].

## Intestinal absorption

Normally, Ca/Sr discrimination occurs under physiological circumstances for the following functions: gastrointestinal absorption, renal excretion, placental transfer, and

Table 2
Radioisotopes of strontium [59]

| Radioisotope | Physical half-life | Characteristics | Use |
|---|---|---|---|
| $^{85}$Sr | 64.8 days | 0.514 keV gamma | Can be used for metabolic studies; scintigraphy and whole-body measurements |
| $^{89}$Sr | 50.5 days | 1488 keV beta radiation | Treatment of bone pain due to metastases from prostatic cancer |
| $^{90}$Sr, decays to $^{90}$Y | 28 years, 64.1 h | 546 keV beta radiation, 2288 keV beta radiation | Contaminant of the biosphere from atomic bomb tests |

mammary secretion [17]. Generally, Sr is poorly absorbed in the intestinal tract. Intestinal Sr absorption in rats decreases with age, but whether this is the case with humans is unknown. Vitamin D promotes intestinal Sr absorption, and Ca inhibits it. Lactose and other carbohydrates can promote both Sr and Ca absorption. Most of the dietary Sr is absorbed from the jejunum, namely, 62% from a liquid dose and 88% from a solid dose in animal experiments. The ratio of absorbed $^{85}Sr/^{45}Ca$ was 0.6–0.7 [33]. The preferential absorption of Ca (discrimination against Sr) might be attributed to the relatively smaller size of the Ca atom. While Ca can be transported from the mucosal to the serosal side against a concentration gradient, this does not seem to be the case for Sr, using an everted gut technique. [65]. However, $^{85}Sr$ could be transported against a concentration gradient from the serosal to the mucosal side. Whether those animal experiments bear any relation to the situation in normal man is another matter, but perhaps Sr absorption from the intestinal lumen to the blood might be entirely passive, while movements of Sr into the intestinal lumen might be active, suggesting some sort of homeostatic regulation of blood Sr at high blood levels.

## Strontium in muscles

Ca directly activated the release of Sr from the sarcoplasmatic reticulum of rat cardiac ventricular myocytes [55] in studies of the effect of Sr ions on Ca-dependent feedback mechanisms during excitation–contraction coupling. In an investigation on the intracellular pathway of the acetylcholine-provoked contraction in cat detrusor muscle cells, Sr which depletes or blocks intracellular Ca release, inhibited acetylcholine-induced contraction [1]. Activation of smooth muscle is normally accompanied by a rise in intracellular $Ca^{2+}$ concentration. Contraction of rat portal vein induced by noradrenaline is lost when $Ca^{2+}$ is replaced with $Sr^{2+}$, which can enter through $Ca^{2+}$ channels and be released from the sarcoplasmatic reticulum [6]. In isolated muscle tissue, 2 mM $Sr^{2+}$ has a $Ca^{2+}$-like action on hexose transport [4]. Whether these observations bear any relation to normal physiological excitation–contraction coupling, or are merely of pharmacological interest remains to be shown.

## Renal handling of strontium

Ca and Sr seem to share a common tubular transport path in the renal tubules [64]. Sr in suspended renal proximal tubular cells inhibited PTH-dependent cyclic AMP production, like did Ca, at concentrations up to 10 mM [37]. The renal clearance of Sr is around three times that of Ca, perhaps due to smaller tubular reabsorption, which again might be due the larger size of the Sr atom vs. that of Ca. This is one of many examples showing that studies with radiostrontium should be used and interpreted with caution when the object of investigation is Ca behaviour.

## Role of strontium in endocrinology

### *Isolated systems*

Sr in many pharmacological investigations using isolated cells or organs often mimics the actions of Ca, although the response to stimulation tends to be weaker. The following examples illustrate this: (A) Sr sustains secretion of insulin as a response to glucose in isolated systems of pancreatic islets, although to a lesser extent than Ca [34]; (B) $Sr^{2+}$ is effective in restoring the insulin-mediated glucose cell uptake after deprivation of $Ca^{2+}$ and $Mg^{2+}$ from the medium in isolated fat cells, but did not substitute fully for Ca and Mg [30]; (C) $Sr^{2+}$ like other di- or trivalent ions inhibits low $Ca^{2+}$-stimulated PTH release, but not in physiological concentrations [8].

### *Whole body investigations*

Sr often acts similarly to Ca. Examples are: (A) pharmacological doses of Sr in pigs augmented calcitonin secretion after infusion into the thyroid artery [19]; (B) in thyroparathyroidectomised rats, calcitonin resulted not only in hypocalcaemia, but also in hypostrontiaemia [20]; (C) glucagon, a known secretogogue of calcitonin, provokes not only hypocalcaemia but also hypostrontiaemia in rats. In one study, minimum value of serum Ca and serum Sr was seen simultaneously on the third day of administration of calcitonin or glucagon [26].

## Strontium in bone

The amount of Sr in the skeleton is only 0.035 of its Ca content [28]. Radiostrontium is cleared from the blood almost immediately after injection. $^{85}Sr$ passes the walls of Haversian capillaries by diffusion to reach bone extracellular fluid [23]. Administered Sr is almost exclusively deposited in bone [43]. Na, Pb, and Sr can be substituted in the Ca positions of apatite [61]. Radiostrontium has been used as a tracer for Ca in kinetic studies although radiocalcium and radiostrontium behave differently, but both have strong bone-seeking properties. Differences can be seen in studies on the rate of urinary excretion and decline of plasma concentration of $^{85}Sr$ and $^{47}Ca$ after intravenous injection in the same individual. Sr and Ca behave similarly, but not identically regarding intestinal absorption, renal excretion, and accumulation into bone. One important difference is that the total amount of Sr in the skeleton is small compared to Ca (Table 1). In contrast to Ba and Ra, which are mainly excreted in the faeces, Ca and Sr are largely excreted by the kidneys after intravenous injection. In long-term studies

after incorporation into bone, the two elements behave almost identically [61]. Morohashi et al. [42] studied the effect of varying oral doses of Sr in rats. They found at constant Ca levels in the diet a significant increase in the Ca content of bones if the animals received 87.5 μmol Sr/day, but doses up to 10 times higher resulted in reduced bone Ca content and hypocalcaemia. In another study, this group demonstrated by kinetic, histomorphometric, and chemical methods that in ovariectomised rats, Sr at a dose of 87.5 μmol/day prevented the increased rate of bone turnover induced by ovariectomy [41]. In vitro studies of osteoblastic cultures confirmed the dose-dependent multiphasic pattern of Sr effect. At 0.5 and 1 μg/ml Sr concentration in the culture medium, a reduced intracellular nodule formation was found (impaired in vitro osteoblast differentiation), at 2–5 μg/ml nodule formation and mineralisation were normal, and at 20–100 μg/ml there was an inhibitory effect on mineralisation (reduced hydroxyapatite formation) [62].

Staub et al. [56] have described a nonlinear compartmental model for Sr based on plasma Sr concentration data collected in postmenopausal women given twice-daily oral doses of strontium ranelate and after discontinuation of the Sr-containing agent. They found good overall agreement of the model predictions at the initial stage including discrimination of Ca over Sr, but their experimental evidence was limited. As has been said in the past for calcium compartmental models, if there is no equilibrium due to diffusion of tracer atoms from the exchange surfaces of bone into unaccessible bone sites where exchange is not possible (e.g. radial diffusion in Haversian bone cylinders), it might be more appropriate to apply a model of an "expanding pool" for the later events after Sr administration [36].

### *Antiosteoporotic effect of strontium*

Low Sr levels have been found in the femoral head which is a frequent site of low-energy fracture [11].

Shorr and Carter [51] showed after giving a moderate dose of strontium lactate that the deposition of Ca in bone was greater than total Ca storage when Ca was given without Sr. This observation might be the first one suggesting that Sr might be useful in the treatment of osteoporosis. A few years later, strontium lactate in a preliminary study was shown to reduce bone pain in patients with osteoporosis with concomitant radiological signs of amelioration [38]. The lack of attention to those observations might be because a rachitogenic effect of higher doses of Sr had been described. Also, the nuclear fallout of radiostrontium and its contamination of the human body became a more important object for investigation for many years, and strontium became synonymous with radioactive strontium.

Reports showed that strontium ranelate depressed bone resorption and maintained bone formation in vivo under certain circumstances [35], increased vertebral bone volume without inducing a mineralisation defect [30], and enhanced bone cell replication and bone formation in vitro [46]. Boivin et al. [5] studied the biodistribution of Sr after administration of strontium ranelate to monkeys by X-ray microanalysis. Changes at the bone crystal level were evaluated with X-ray diffraction and Raman microspectroscopy. Sr was dose-dependently incorporated into bone mineral of both trabecular and compact bone, mainly into new bone, and mainly into trabecular bone. When the agent was withdrawn, Sr concentration in bone decreased rapidly, a feature which distinguishes this agent which has now been developed as a drug, from bisphosphonates, which remain in bone forever. No changes in the crystal lattice, in crystallinity, or crystal structure were observed. Less than one Ca ion out of 10 was substituted for by one Sr ion in each crystal. Long-term studies in rats confirmed pronounced dose-related increments in trabecular bone volume, mineralised bone volume, osteoblastic surface, and a reduction in osteoclast number, but osteoid thickness was not affected [24].

### *Strontium ranelate*

Recently, the preliminary results of an extensive multicentre study on the effect of strontium ranelate in postmenopausal osteoporosis have been published. They showed very pronounced reduction in the incidence of hip fractures and vertebral compression fractures [39,40,49]. Strontium ranelate enhances bone cell replication and bone formation in vivo [12]. The rather unique action of strontium ranelate as an osteoblast agonist [34] could be explained by an activation of a Ca sensing receptor. Such receptors have been identified in different cells of the body inclusive of osteoblasts. It seems that $Sr^{2+}$ is an agonist of the calcium sensing receptor in bone, although with somewhat lower affinity than $Ca^{2+}$ [9]. Recent evidence suggests that a cation sensing receptor in osteoblasts, which is activated by Sr, may be functionally different from other Ca sensing receptors [48].

### *Rachitogenic effect of strontium*

Sr is less toxic than Ca in farm animals [58]. However, high amounts of dietary Sr can induce bone changes similar to rachitic lesions in experimental animals, especially if Ca intake is low [2,15,16]. This seems to be caused by a combination of impaired intestinal absorption of Ca and reduced renal production of 1,25-dihydroxy cholecalciferol. The direct effects of Sr on intestinal Ca absorption seem to be caused by the fact that the two metals share a common absorption pathway, combined active and passive transport mechanisms favouring Ca absorption. The competitive inhibition has been demonstrated in both isolated intestinal slices and perfused intestines. It has been demonstrated that that Ca-binding protein binds Sr to a lesser degree than Ca [44,50], and that Sr inhibits the kidney 1-hydroxylase, impairing the production of 1,25-$(OH)_2$ vitamin $D_3$ [45,46]. In a later publication, it

was reported that in chicken Vitamin $D_3$, as well as its 24-hydroxy derivative lost its antirickets activity at high dietary Sr concentrations, but 1,25-dihydroxy vitamin D retained its ability to induce calcium binding protein synthesis in intestinal epithelium and to some extent to stimulate bone mineralisation [3]. High Ca diet as well as high Sr diet in pregnant mice reduced the content of calcium binding protein in both the maternal intestine and placenta. Eventually, this would lead to hypomineralisation of the foetal skeleton. [10]. Animal studies suggest that young animals are more sensitive to excess Sr than old animals, and that inadequate intake of Ca and vitamin D increases the harmful effects on bone [60].

An observation of human nutritional importance was published by Ozgur et al. [47]. They found that in two regions of Turkey where the amount of soil Sr was highly different, the prevalence of rickets was too high: in region 1, the Sr content was above 350 ppm and in region 2 less than 350 ppm. In region 1, the prevalence of rickets was 31.5% and in region 2 it was 19.5%. Thus, it seems that high concentration of soil Sr can induce rickets, although lack of sunshine and dietary deficiency might contribute.

A direct effect of high doses of Sr in bone in vitro was demonstrated by Verberckmoes et al. [62] who found evidence of deficient hydroxyapatite formation at high medium doses of Sr, perhaps an analogue to the situation in dialysis patients, who create special problems of osteomalacia. Although the prevalence of osteomalacia has been reduced in recent years, dialysis patients with osteomalacia do exist in a proportion of <5%. They are known to have elevated bone Sr concentrations and high Sr/Ca ratios in bone perhaps due to high concentrations of Sr in the dialysis fluid [13,14]. However, end-stage renal failure patients not yet on dialysis had normal bone strontium levels, but a high prevalence of osteomalacia [54].

## Homeostatic control

It appears from animal studies that Sr can substitute for Ca in many physiological processes. These include muscular contraction and blood clotting, which are provoked by Sr as well as by Ca, but to a lesser degree. It seems that whenever there is an active transport across biological membranes, for example, in gastrointestinal absorption, renal excretion, lactation, and placental passage, Ca is transported more easily than Sr [58].

Conversely to Ca, Sr is not under homeostatic control in the sense that its total amount in the body and its level in biological fluids, for example, the blood is kept strictly constant by an accurate feedback mechanism. This was a statement made in the early 1960s, before the age of calcitonin and the active vitamin D metabolites 25-hydroxy cholecalciferol or 1,25-dihydroxy cholecalciferol, and so far nothing has proved it to be wrong. This does not exclude the possibility that Sr levels can be influenced by Ca and by hormones. It is well known that in mammals, extracellular fluids have millimolar concentrations of Ca and micromolar concentrations of Sr. At this high Ca/Sr molar ratio, Sr cannot compete with Ca, and there has during evolution been little need for selection of separate mechanisms specific for Ca and Sr. On a molar basis, Sr seems less biologically active than Ca, and toxicity of Sr is not pronounced [60]. Thus, parenteral administration of Sr giving rise to large increments of serum Sr is possible without deleterious actions on organs or functions. It may well be that intracellular Sr is more strictly regulated than extracellular Sr, but little is known about this.

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