WHITE PAPER

# Strontium: Still a Viable Therapy for Bone Health

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# Strontium: Still a Viable Therapy for Bone Health

The use of oral strontium compounds to improve bone strength and reduce fracture risk has proven to be quite successful over the past few decades, established using experiments in both humans and animals. These clinical results align with a host of basic scientific research showing numerous mechanisms by which strontium modulates bone architecture and metabolism. Nonetheless, the use of oral strontium compounds for improving bone strength is controversial amongst some clinicians for a variety of reasons. In this whitepaper we will discuss the data, for and against, the use of oral strontium therapies for bone-building purposes in subjects that are at-risk for fractures; including therapeutic conundrums that arise when successfully using strontium. We maintain that strontium compounds can be safe adjunct therapies for improving bone strength in most subjects at risk for increase fractures due to poor bone strength. However, as with any therapeutic agent, it is not recommended for all subjects with low bone mineral density or as a general bone-building nutrient. Understanding the therapeutic benefits of oral strontium, including common misconceptions about its clinical use, is important if clinicians are to leverage this unique therapeutic mineral.

## Brief Overview of Strontium's Therapeutic Use for Bone Health

Strontium (Sr) is an alkali earth metal, with characteristics very similar to that of calcium; though having an atomic weight nearly double that of calcium. First discovered in the 18th century, this trace element is found in ground water, ocean water and in various foods such as leafy green vegetables and some seafood. The ability for Sr to naturally accumulate in the bones of animals after being fed small doses was first published in 1870.[1,2] However, it wasn't until the 1950s that human studies were first published; most notably McCaslin and Jane's case series of subjects given strontium lactate (6.4 grams/day in divided doses- delivering 1.7 grams/day of Sr) published in the Mayo Clinic Proceedings in 1959.[3] They concluded their study by saying "*A study has been made of the case records of 32 patients treated for osteoporosis with strontium lactate, or strontium lactate with hormones, and then traced for various periods with repeated physical and roentgenographic examinations. Marked subjective improvement was experienced by 84 per cent of the patients. Although the mechanism of action of strontium lactate in the treatment of osteoporosis remains to be elucidated, the therapeutic value of the drug appears to be established.*"

However, it would be another four decades before the use of strontium would become a common therapy for osteoporosis, with the approval of the patentable compound Sr Ranelate (as Osseor® / Protelos® / Protos®) in Europe and elsewhere.[†] Sr Ranelate is a compound formed from two molecules of strontium with ranelic acid, which delivers 340 mg of elemental strontium in every gram. The approval of Sr Ranelate was based upon a series of highly successful Phase 2 and Phase 3 clinical trials published between 2002-2005; along with a host of animal studies and mechanism studies published in the preceding years.[4,5,6,7] These studies provided strong evidence for Sr ranelate's anti-fracture benefits, which was associated with Sr accumulation in bone and increased bone mineral density (BMD).[8,9] Subsequently, Sr Ranelate was considered a first-line therapy for anti-fracture therapy in post-menopausal women in many of the countries where it was approved.

## Strontium as a Dietary Supplement: Efficacy and Safety Evaluations

A variety of strontium compounds have been used as dietary supplements in the past, most notably strontium citrate (~34% Sr by weight) in the United States, but also Sr lactate, Sr carbonate, and Sr chloride. When Sr Ranelate was approved in Europe for osteoporosis, the use of these compounds as dietary supplements increased in the US as the demand for strontium supplementation increased. However, unlike Sr Ranelate which has been evaluated (for efficacy and safety) in numerous large clinical trials, these unpatented forms have only been tested in

[†] Strontium Ranelate was never approved as a drug in the US.

a variety of *in vitro* mechanistic studies, animal studies or small human clinical trials and case reports. Nonetheless, when these studies are combined with the proposed and known mechanisms of action for strontium, they provide sufficient evidence to suggest that these Sr forms are likely to function in the same manner as Sr ranelate for building BMD and reducing fracture risk (assuming they deliver an equivalent dose). In other words, the benefit of Sr Ranelate is in its ability to deliver strontium; no mechanism for bone strengthening have been attributed to ranelic acid/ranelate (which simply disassociates from Sr in the GI tract). Listed here are some key pieces of evidence that have allowed us to arrive at this conclusion.

- While there are a variety of proposed mechanisms for how strontium strengthens bone density and strength, including the modulation of both osteoclast and osteoblast activities; the direct incorporation of Sr molecules into the bone matrix itself appears to be one of the keys to its therapeutic benefit.[10,11]
- Accumulation of Sr in bone after oral ingestion[†] (often with measurable improvement in bone strength) has been documented for Sr lactate, Sr Citrate, Sr Carbonate, Sr Chloride, of course, Sr Ranelate.[3,12,13,14]
- Animal studies comparing oral Sr Ranelate with Sr Citrate show that oral Sr from citrate incorporates into bones at a similar (or higher) level than Sr delivered as Sr Ranelate.[15]
- The use of radiolabeled Sr (in the form of Sr chloride) is used as a bone-accumulating agent for palliative treatment for patients with bone metastases. While this is not intended for anti-osteoporotic effects, it confirms the well-established bone-accumulating properties of Sr delivered in a salt form.[16]
- Strontium incorporation into bone and dental implants (via biocomposites) has been shown to improve osseointegration, confirming a direct biomechanical effect of strontium in bone formation. This is particularly enhanced in osteoporotic models.[17,18]
- Using instrumental neutron activation analysis (INAA), bones from subjects consuming Sr show improve microarchitecture compared to Sr-naïve subjects.[19]
- Human studies show Sr continues to accumulate in bone even after years of oral supplementation with Sr Citrate.[20]
- Strontium citrate improved the formation of new bone in the current rabbit model of mandibular distraction osteogenesis.[21]

## Safety Concerns Raised for Sr Ranelate[22]

In 2013, the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) noted concerns over cardiac safety emerging from annual periodic safety update reporting (the mechanism whereby manufacturers submit regular safety data to the EMA) and subsequently recommended a reappraisal of the overall benefit-risk ratio of strontium ranelate.[23,24] The pooled analysis in 7572 postmenopausal women (3803 strontium ranelate and 3769 placebo) indicated an increased risk for myocardial infarction (MI) with strontium ranelate, with estimated annual incidences of 5.7 cases per 1000 patient years versus 3.6 cases per 1000 patient years with placebo. The odds ratio for MI was 1.60 (95% CI: 1.07, 2.38) for strontium ranelate versus placebo (incidences of 1.7 versus 1.1%, respectively). Interestingly, among the cases of MI, fatal events were less frequent with strontium ranelate (15.6%) than with placebo (22.5%).

However, post-marketing surveillance data covering > 3.4 million patient years of treatment from September 2004 to February 2013 did not support an increased risk of MI.[25] Subsequent observational studies with very large populations have similarly not indicated any adverse signal. Thus, a prospective observational cohort study of 12,076 patients on strontium ranelate did not demonstrate increased risk of cardiac events over the 32.0 ± 9.7 months of follow-up.[26] In a nested case-control study of 112,445 women with treated postmenopausal osteoporosis, of whom 6487 were receiving strontium ranelate, the annual incidence rates for first definite MI, MI with hospitalization and cardiovascular death were 3.24, 6.13, and 14.66 per 1000 patient years, respectively. As expected, in this analysis within the UK Clinical Practice Research Datalink (CPRD), obesity, smoking and cardiovascular treatments were associated with greater risk of cardiac events, but current use or past use of strontium ranelate was not associated with increased risk for first definite myocardial infarction (compared with patients who had never taken strontium ranelate) [OR: 1.05 (95% CI: 0.68, 1.61) and 1.12 (95% CI: 0.79, 1.58), respectively], hospitalization with myocardial infarction [0.84 (95% CI: 0.54, 1.30) and 1.17 (95% CI: 0.83, 1.66)], or cardiovascular death [0.96 (95% CI: 0.76, 1.21) and 1.16 (95% CI: 0.94, 1.43)].[27]

[†] These and other forms have also been used for creating medical devices/implants, which deliver Sr to bone. This application strongly confirms our argument, but is outside the scope of this review.

 

The most recent study combined data from three multinational multi-database sources to undertake case-control studies nested within a cohort of new users of strontium ranelate or bisphosphonates.[28] Cases of acute myocardial infarction, venous thromboembolism or cardiovascular death were matched with up to ten controls by sex, year of birth, index date and country. The results indicated that there was no apparent excess risk of acute myocardial infarction with current strontium ranelate versus current bisphosphonate use [Odds Ratio: 0.89 (95% CI 0.70, 1.12)] nor with current versus past strontium ranelate use [0.71 (95% CI: 0.56, 0.91)]. There was evidence for an increased risk of venous thromboembolism with current strontium ranelate compared with current bisphosphonate use [1.24 (95% CI: 0.96, 1.61)], and current versus past strontium ranelate use [1.30 (95% CI: 1.04, 1.62)]. Cardiovascular death was more common with current strontium ranelate versus current bisphosphonate use [1.35 (95% CI: 1.02, 1.80)]. However, when current use was compared with past strontium ranelate use (which better controls for confounding by indication) a reduced risk of cardiovascular death was apparent [0.68 (95% CI: 0.48, 0.96)]. Importantly, this study was undertaken after the change in label and specification of cardiovascular disease as a contraindication to strontium and late use. Cessation of therapies during end-of-life care and residual confounding by indication are suggested by the authors to potentially partly explain these apparently discrepant findings.

Nonetheless, while Sr Ranelate was never banned in Europe (a common misunderstanding), Servier ceased the distribution of the drug in 2017 due to poor sales and use. However, the drug company Aristo began distributing Sr Ranelate in 2019, and it is again available in some countries where it had been previously approved for use.[29]

## What About DXA Scan Anomalies?

One of the most common criticisms related to the use of Sr Citrate (or any strontium compound for that matter) is that, because strontium atoms are heavier than calcium, the increases in BMD detected using DXA (Dual X-Ray absorptiometry) are simply a therapeutically-inert technical artifact.[30] In fact this issue has been investigated by several groups over the years and it is generally agreed that for every 1% increase in the molar percent of Sr within bone, there is a 10% overestimation of BMD when using a normally calibrated DXA measurement (an estimate that can vary depending on the DXA machine being used).[31,32] This has several implications for the clinician using oral strontium supplementation of any kind. First, the ability to predict how much of any particular BMD measurement by DXA is "overestimation" requires one to know the %Sr within the bone being measured by DXA, something that is not easily done using non-invasive techniques. Using dual-photon absorptiometry (DPA) and DXA, researchers from Denmark discovered that there was a predictable increase in Sr content (measured in the radius) based on the length of time and dose that each person had been consuming Sr Ranelate (these were subjects from other Sr Ranelate trials).[33] Using this analysis, the mean %Sr in subject consuming Sr for over 7 years (most of whom were consuming 2g/day SrRanelate) was only 1.1% Sr in the distal radius. However, as they point out in their discussion, calcium and strontium incorporate at different rates in different subjects and at different skeletal locations within each individual, making it difficult to extrapolate Sr incorporation to each area used for DXA measurements (assuming one had access to a DPA at all).

While this phenomenon can be frustrating, in that once strontium supplementation is initiated it is difficult to use uncalibrated DXA scoring to accurately predict BMD, it is important to ask whether the clinician is attempting to strengthen the patient's bones and reduce their risk for fractures, or manage DXA scan scores. In fact, we would argue that even if some of the density increases are "artifact" from strontium incorporation, this acts as an objective measure that Sr is indeed incorporating into bone tissue; something that has been shown to improve architecture and strength.

## Conclusions and Recommendations

Today's clinicians have many nutritional and lifestyle options for improving bone strength, many of which act synergistically to promote healthy bone turnover and prevent fracture risk. As a therapeutic mineral, strontium may play a strategic role in optimizing bone-building therapies. However, unlike these other nutrients, we believe strontium should be reserved for subjects who are well past building their peak bone mass and are experiencing loss of bone mineral density due to aging. Generally, this includes postmenopausal women with osteopenia or osteoporosis (upon which most oral strontium research has been done); or similarly aged men with low BMD. Likewise, since most clinical studies using oral strontium therapy also included calcium and vitamin D, we also recommend that calcium supplementation (~800 mg daily) and vitamin D (>2,000 IU/day) be given when using oral strontium therapy. Where possible, the consumption of strontium and calcium should be separated as they compete with one another during gastrointestinal absorption. Based upon the published literature, we believe strontium citrate is likely to be safe in most subjects; as safe as calcium citrate at similar doses (recalling that calcium supplementation without the use of vitamin D has itself been linked with increased risk for cardiovascular events).[34]

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