

# Strontium Ranelate Using for the Treatment of Postmenopausal Osteoporosis



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## Abstract

The main reason of postmenopausal osteoporosis is high bone turnover due to increased osteoclastic action. Strontium Ranelate is a new drug that is used for the treatment of postmenopausal osteoporosis. We searched PubMed in May 2016 using the terms 'Strontium ranelate' for experimental study and review articles. The result from the studies that we have conciliated show: Strontium ranelate enhances bone resistance and increases the bone formation. Strontium ranelate has been shown to increase bone apposition rates and bone mineral density while maintaining the quality of bone mineral; but it has no effect on mineralization. Evidence from in vitro and in vitro studies present the evidence that strontium ranelate is able to inhibit the osteoclasts resorbing activity, decreased osteoclastic differentiation (Prevention of differentiation of blood monocyte and pre-osteoclasts into osteoclasts) and increase apoptosis of osteoclasts. The studies show that strontium ranelate increased pre-osteoblastic replication and osteoblastic proliferation and differentiation as evaluated by the measurement of DNA synthesis in osteoblasts.

Strontium ranelate stimulated the synthesis of PG by human chondrocytes. Strontium ranelate promotes the synthesis of PG capable of integrating the ECM. It has been show that post fracture use of strontium ranelate on the ovariectomized rats is associated with better fracture healing as assessed by radiography, histological analysis and biomechanical testing. The exact mechanism by which strontium ranelate exerts these effects is not definitely understood, but may include inhibition of osteoclast formation and stimulation of osteoblast proliferation. In most cases use of strontium ranelate did not seem to be associated with series adverse events and most adverse events were mild and transient. It seems that Strontium ranelate is a effective and winsome treatment for osteoporosis and in the most cases the side effect of this drug is negligible.

**Abbreviations:** SOTI: Spinal Osteoporosis Therapeutic Intervention; TROPOS: Treatment of Peripheral Osteoporosis; STRATOS: Strontium Ranelate for Treatment of Osteoporosis; PREVOS: Prevention of Osteoporosis

## Introduction

The main reason of postmenopausal osteoporosis is high bone turnover due to increased osteoclastic action [1]. Strontium Ranelate is a new drug that is used for the treatment of postmenopausal osteoporosis [2]. It is used for decreasing the risk of fracture in vertebral and non-vertebral (especially hip) bones [3]. Strontium ranelate is a combination of strontium chloride ( $\text{SrCl}_2 \cdot 6\text{H}_2\text{O}$ ) and sodium ranelate [4]. Strontium ranelate contains two stable atoms, strontium and one organic carrier, ranelic acid [5]. The molecular action mechanism of strontium ranelate is not understood [4]. But its action mechanism on bone is complex and time-dependent and dose- dependent [6]. It has been seen that the low doses of strontium ranelate persuaded the bone tissue quality [7]. It enhances bone tissue quality, and is effective on bone resistance and reduces

the fracture risk in postmenopausal osteoporotic patients which treated with strontium ranelate [8].

Strontium ranelate also prevents bone loss that is induced by estrogen deficiency in postmenopausal women by restraint of bone resorption and stimulation of bone formation [9]. In ovariectomized rats, Strontium ranelate prevented bone resorption, whereas bone formation remained elevated [10]. This drug is well tolerated because it has no effect on food intake or body weight [11]. Strontium ranelate has some similarities with  $\text{Ca}^{+2}$  in its absorption in the digestive system, incorporation into bone, and reabsorption in the kidneys [12]. Because strontium, a divalent cation like  $\text{Ca}^{+2}$ , it's possible that the ranelate salt plays a role in the incident of this reaction [13]. Administration of 2 g/day of strontium ranelate to

postmenopausal women for a 2-year resulted in uncoupling between bone resorption and bone formation that led to a significant increase in the lumbar spine bone density and a 44% reduction in vertebral fracture during the 2nd year of treatment [14]. The strontium ranelate effects on bone can be studied by histomorphometry, DXA, and biomechanics in preclinical studies [15]. Originally strontium was detected in the 1700, in Scotland, a place near Strontian [16]. This earth element is present in food and water and throughout the bones [17]. Strontium ranelate was used widely in the 1950 for the treatment of malignant bone diseases, osteoporosis, painful, etc. [18].

## Material and Method

We searched PubMed in May 2016 using the terms 'Strontium ranelate' for experimental study and review articles. Of the 61 articles retrieved, there were 5 review articles. Evidence of the safety and efficacy of strontium ranelate comes from two large multinational clinical trials, the Spinal Osteoporosis Therapeutic Intervention (SOTI), [5] and Treatment of Peripheral Osteoporosis (TROPOS), [19] studies, which were designed to study vertebral and non vertebral fractures respectively; and clinical data is available from 2 earlier Phase 2 trials, the Strontium Ranelate for Treatment of Osteoporosis (STRATOS), Meunier et al. and Prevention of Osteoporosis (PREVOS), [18] studies.

## The Effects of Strontium Ranelate on Bone

Strontium ranelate cause a positive bone balance in experimental models [13]. It has a unique effect on bone remodeling by increasing bone formation and decreasing bone resorption, which leads to prevention of bone loss and increase in bone mass and strength [20]. It increases markers of bone formation and also has anabolic effects on bone [21]. The analysis of bone markers showed that strontium ranelate reduced the excretion of the bone resorption marker from kidney and increased the levels of osteoblast differentiation serum marker, bone-specific alkaline phosphatase [22]. Strontium ranelate enhances bone resistance and increases the bone formation, as evaluated by increased ALP activity, and it is confirmed by the increased trabecular and cortical bone tissue amount [23].

Strontium ranelate has been shown to increase bone apposition rates and bone mineral density while maintaining the quality of bone mineral [24]; but it has no effect on mineralization [25]. Actually some studies on intact animals confirm that strontium ranelate preserves the structure of bone matrix crystals without affecting the mineralization process [26]. It has been shown that treatment with strontium ranelate results in the formation of lamellar bone with no evidence of mineralization defect or other deleterious effects [27].

a) It has shown strontium ranelate increase the diameter of the bone shaft suggesting an effect on periosteal bone formation [28]. It also increases trabecular bone volume, trabecular number, trabecular thickness, and cortical thickness Arlot et al. Modification of bone diameters with periosteal apposition may effects bone strength of long bones [29]. This effect on bone size is very important and can play a role in the improve-

ment of mechanical properties of bone, because the diameter of long bones predicts to 55% of the variance of the bone strength (Arlot et al 2008). Strontium ranelate treatment seems to stimulate both trabecular and cortical bone formation in 3D analyses but without increase of cortical porosity [30]. The change in 3D trabecular and cortical micro architecture improve bone biomechanical properties Arlot et al.

b) Evidence from in vitro and in vitro studies present the evidence that strontium ranelate is able to inhibit the osteoclasts resorbing activity [31], decreased osteoclastic differentiation (Prevention of differentiation of blood monocyte and pre-osteoclasts into osteoclasts) and increase apoptosis of osteoclasts [5]. Strontium ranelate inhibited the expression of two osteoclast markers: the  $\alpha$  subunit of the vitronectin receptor and carbonic anhydrase-II in bone marrow culture [32].

c) The studies show that strontium ranelate increased pre-osteoblastic replication and osteoblastic proliferation and differentiation as evaluated by the measurement of DNA synthesis in osteoblasts [9]. It stimulates osteoblastic differentiation markers activity such as ALP, bone sialoprotein and osteocalcin in osteoblasts [16]. Strontium ranelate promote osteoblasts survival [33] and its positive effects on osteoblast survival, is because of the seven-transmembrane-spanning extracellular calcium-sensing receptor which is expressed by osteoblasts and that responds to strontium [34]. However, recently it has been showed which Strontium ranelate increases osteoblasts survival independently of the calcium-sensing receptor, indicate that other signaling mechanisms may involve in the positive effects of Strontium ranelate on osteoblastogenesis [35].

d) Some in vitro Studies in human osteoblasts suggest that strontium ranelate have the ability to promote the differentiation and survival of osteocytes, which is an additional mechanism of its anti-fracture efficacy [10].

e) Strontium ranelate has beneficial effects on both cartilage and bone remodeling Henrotin et al. It has shown evidence of beneficial effects of strontium ranelate on interference in cartilage metabolism [36]. It stimulates cartilage matrix formation by ionic stimulation of chondrocyte anabolism without affecting resorption of cartilage; it enhanced collagen synthesis and has a direct effect on proteoglycan synthesis [37]. It could restore the imbalance between chondroresorption and chondroformation observed.

f) Strontium ranelate stimulated the synthesis of PG by human chondrocytes [38]. Strontium ranelate promotes the synthesis of PG capable of integrating the ECM [39]. It also promoted the synthesis of high-molecular weight PG complexes [40]. The mechanism that strontium ranelate influenced the synthesis of PG is not known until now Henrotin et al. Strontium is effective in reversing the IGF-I stimulating effect, because factors which lead to increase the synthesis of PG were reported as causing an initial decrease in cytosolic free Ca concentration [41]. IGF-I stimulation of PG synthesis maybe increased by

strontium ranelate treatment [42]. This effect may be consequent to the proliferation of chondrocyte because IGF-I is required for cell proliferation [43]. This fact that IGF-I regulates the metabolism of chondrocyte (by IGF-I produced in response to a high of strontium) can be responsible for the PG increase [44]. Furthermore high extra cellular Ca concentration increases the secretion of IGF-I as well as the expression of IGF-I mRNA by osteoblastic MC3T3-E1 cells [45]. This finding can explain why strontium ranelate increased the IGF-I effect when it was added to a low concentration [36].

**Fracture Healing:** Although antifracture efficacy of strontium ranelate has been demonstrated, there is paucity of data on the effect of strontium ranelate on fracture healing [4] and there are limited data about the effect of strontium ranelate on fracture healing Seeman et al. It has been show that post fracture use of strontium

ranelate on the ovariectomized rats is associated with better fracture healing as assessed by radiography, histological analysis and biomechanical testing Seeman et al. Some of scientists evaluated the efficacy of strontium ranelate on fracture healing in healthy bone Roux et al. In these studies employing traumatically induced fracture, no effect on fracture healing were reported Arlot et al. & but Li et al. reported that 625 mg/kg/day strontium ranelate revealed beneficial effect on the fracture healing on the ovariectomized rats [24]. The weaker antiresorptive activity of strontium ranelate can not disrupts the osteoclast resorption in the remodeling phase [19]. Anabolic activity of strontium ranelate can provide beneficial effect on the regenerative and reparative processes of the remodeling phase in the fracture healing (Roux et al 2016). Further studies are needed to discover the precise mechanism of action of strontium ranelate on fracture healing [19] (Table 1).

**Table 1:** the results of different study about strontium ranelate.

No	Scientist	Year	Model	Result
1	Farlay	2005	<i>In Vivo</i> /Monkeys	Confirming the positive histomorphometric change in bone structure
2	Seeman et al. [5]	2006	<i>In Vivo</i> /Women	Safely reduces the risk of vertebral and non-vertebral fractures
3	Henrotin	2001	<i>In Vitro</i>	Stimulated PG production, Increased the stimulatory effect of IGF-I (1029 M) on PG synthesis, Stimulates human cartilage matrix formation
4	Ammann et al. [4]	2007	<i>In Vivo</i> /Rats	Direct action on bone tissue quality, Improves bone tissue quality, Increase in bone strength, Reduction of fracture risk
5	Roux et al. [5]	2006	<i>In Vivo</i> /Women	Anti-vertebral fracture efficacy
6	Bolland mj & greya [13]	2014	Librarian	The risks of strontium use are similar to the benefits
7	Seeman et al. [5]	2008	<i>In Vivo</i> /Women	Reduces the risk of vertebral fractures
8	Reginster et al. [3]	2016	<i>In Vivo</i> /Women	Significant effect on structure in patients with knee osteoarthritis
9	Kaufman et al. [22]	2013	<i>In Vivo</i> /Men	Treatment of osteoporosis in men.
10	Grosso	2008	Librarian	No evidence of aforementioned potentially life-threatening adverse events.
11	Carvalho	2011	<i>In Vivo</i> /Women	rapid bone anabolic effect on unhealed atypical fractures
12	Arlot	2008	<i>In Vivo</i> /Women	Higher mineral apposition rate , Borderline higher in cortical bone, Osteoblast surfaces were significantly higher, Significant changes in micro architecture, Higher cortical thickness and trabecular number, Lower structure model index and trabecular separation, No change in cortical porosity, Enhance bone biomechanical competence, Decreased fracture rate
13	Brennan et al. [24]	2009	<i>In Vitro</i>	Anti-fracture effect, anabolic and anti-resorptive actions
14	Borgstrom	2006	<i>In Vivo</i> /Women	Strontium ranelate is cost-effective in the treatment of postmenopausal women with low BMD
15	Reginster et al. [19]	2005	<i>In Vivo</i> /Women	Significantly reduction of the risk of all non-vertebral and hip fractures, strontium ranelate offers a safe and effective means of reducing the risk of fracture associated with osteoporosis
16	Roux	2016	<i>In Vivo</i> /Women	Vertebral antifracture efficacy, Efficacy of antiosteoporotic
17	Ammann et al. [4]	2004	<i>In Vivo</i> /Rats	Improves bone resistance, Increasing bone mass, Improving architecture, Maintaining bone stiffness
18	Reginster	2008	<i>In Vivo</i> /Women	Reduction in the incidence of osteoporotic nonvertebral fractures
19	Meunier et al. [5]	2004	<i>In Vivo</i> /Women	Reductions in the risk of vertebral fractures
20	Bruyere	2007	<i>In Vivo</i> /Women	Increase in femoral neck BMD Reduction in vertebral fracture incidence
21	Choudhary et al. [16]	2007	<i>In Vitro</i>	Significantly increased ALP activity, Increased ALP and OCN mrna expression, Increased mineralization after, Dose-dependently increased PGE2 production, Stimulation of mineralization





Some nervous system disorders, including disturbed consciousness, seizures, mental impairment, and memory loss and were reported with the use of strontium ranelate [57]. Strontium ranelate is associated with a number of other risks, such as serious disturbances in consciousness, liver inflammation, seizures, gastrointestinal disturbance, reduced number of blood cells, severe skin reactions such as Stevens–Johnson syndrome, toxic-epidermal necrosis, and drug rash with eosinophilia and systemic symptoms [58]. In the cases that we should not use strontium ranelate like stroke and ischemic cardiac events we can use efficacious drugs such as alendronate, risedronate, zoledronate, or denosumab [18]. Strontium ranelate acts through an innovative mode of action by inhibiting bone resorption and stimulating bone formation [59]. Strontium ranelate is a new drug for the treatment of postmenopausal osteoporosis and its safety profile is not fully established [60]. Strontium ranelate has been associated with adverse events and idiosyncratic reactions [61]. Strontium ranelate has been studied in many studies for a longer duration. So, its pre-marketing safety data are relatively robust [49].

## Conclusion

It seems that Strontium ranelate is effective and winsome treatment for osteoporosis and in the most cases the side effect of this drug is negligible.

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