Strontium ranelate improves bone microarchitecture in osteoporosis

Neveen A. T. Hamdy

In osteoporosis, disruption of bone remodelling leads to bone loss, microarchitectural damage and increased fracture risk, and the goal of any treatment for osteoporosis is to decrease this fracture risk. Available anti-resorptive and anabolic agents effectively achieve this goal by either suppressing or stimulating the activation frequency of bone remodelling units, and by improving the biomechanical properties of bone by a number of different mechanisms. Strontium ranelate represents a novel approach in the management of osteoporosis with proven anti-fracture efficacy. Two putative mechanisms have been proposed for the unique dual mode of action of strontium ranelate, rebalancing bone turnover in favour of bone formation: activation of the calcium-sensing receptor, and increase in the expression of osteoprotergerin (OPG), coupled with a decrease in RANK ligand expression by the osteoblasts. In addition to these cellular changes, micro-CT analysis of bone biopsies from strontium ranelate-treated patients demonstrate improvement in intrinsic bone tissue quality as evidenced by increased trabecular number, decreased trabecular separation, lower structure model index and increased cortical thickness, associated with a shift in trabecular structure from rod-to plate-like configuration compared with controls. This review examines the evidence for the ability of strontium ranelate to improve bone microarchitecture in osteoporosis and explores the cellular and microstructural changes by which its anti-fracture efficacy may be achieved. No attempt is made at comparing the effects of strontium ranelate on bone microarchitecture with that of other anti-resorptive or anabolic osteoporosis agents.

Key words: Bone mineral density, Bone quality, Bone strength, Bone biopsy, Bone histomorphometry, micro-CT analysis, Dual mode of action, Calcium-sensing receptor, RANK/RANKL/OPG pathway.

Introduction

Bone is a unique living tissue with an infinite capacity for renewal and repair through the dynamic process of bone remodelling, which maintains the material and architectural properties of bone, which in turn determines bone strength and competence. The most important consequence of a disruption in the process of bone remodelling is bone loss and microarchitectural damage in the form of thinning and loss of trabeculae, thinning of the cortex and accumulation of micro-damage. An imbalance in the finely tuned process of bone resorption and formation represents the essence of the pathogenesis of bone loss in all forms of osteoporosis: postmenopausal, age-related, glucocorticoid-induced or due to other secondary causes [1–6].

Traditional approaches in the management of osteoporosis

The goal of any treatment for osteoporosis is to improve bone strength, thereby decreasing fracture risk. The last two decades have witnessed the development of a number of therapies effective in achieving this goal. These therapies have largely targeted bone remodelling, increasing bone mass by either significantly suppressing bone resorption, and also bone formation resulting in overall suppression of bone turnover using anti-resorptive agents such as bisphosphonates, or significantly stimulating bone formation, and also bone resorption, resulting in overall stimulation of bone turnover using anabolic agents such as recombinant parathyroid hormone 1–34 and 1–84 [6–10]. Acting on bone remodelling in diametrically opposite ways, both anti-resorptive and anabolic approaches to the treatment of osteoporosis have been shown to significantly decrease the risk of fracture by improving the biomechanical properties of bone by a number of different mechanisms [6–13]. The optimal level of bone turnover that would maintain the material and structural properties of bone with ageing, including its ability to respond to mechanical loading is, however, yet to be determined [4, 5].

Strontium ranelate is a novel paradigm in the management of osteoporosis by its unique dual mode of action, which rebalances bone turnover in favour of bone formation. The aim of this review is to examine the evidence for the ability of strontium ranelate to improve bone microarchitecture in osteoporosis as a potential significant component of its anti-fracture efficacy [14–21]. The cellular and microstructural changes by which this anti-fracture efficacy may be achieved are also explored.

Evidence for the dual mode of action of strontium ranelate

Evidence from clinical data

Changes in bone markers: Spinal Osteoporosis Therapeutic Intervention and TREatment Of Peripheral OSteoporosis studies. Data from the Spinal Osteoporosis Therapeutic Intervention (SOTI) study, which evaluated the efficacy of strontium ranelate in reducing the incidence of vertebral fractures [14], demonstrated a simultaneous increase of 8.1% in serum bone-specific alkaline phosphatase, a marker of bone formation, and a decrease of 12.2% in serum C telopeptide cross-links of type I collagen, a marker of bone resorption at the third month of treatment compared with placebo (P < 0.001). These changes were sustained from the third month of treatment onwards to 3 years of treatment. Similar changes were also observed in the TREatment Of Peripheral OSteoporosis (TROPOS) study, which evaluated the efficacy of the agent in reducing the incidence of non-vertebral fractures [15, 22]. The dissociate changes in markers of bone formation and resorption suggest an uncoupling effect of strontium ranelate on bone remodelling.

Histomorphometric analysis of bone biopsies: SOTI, TROPOS and STRontium Administration for the Treatment of OSteoporosis studies. Histomorphometric analysis of unpaired transiliac bone biopsies was conducted in a subset of postmenopausal women with osteoporosis participating in the SOTI, TROPOS and STRontium Administration for the Treatment of OSteoporosis (STRATOS) studies, the latter investigating the efficacy and safety of different doses of strontium ranelate in osteoporosis [23, 24]. The bone biopsies were obtained...
from patients who were treated with strontium ranelate (n = 49) or placebo (n = 89) for a duration of 1–5 years before being biopsied [24]. In the strontium ranelate-treated group, there was a significant increase in bone formation parameters, as evidenced by a significant increase in osteoblastic surfaces (+38%; \( P = 0.047 \)), and in mineral apposition rate, in both cancellous and cortical bone (+9%; \( P = 0.019 \) and +10%; \( P = 0.056 \), respectively) in treated compared with untreated patients. There was no change in activation frequency and mineralization was preserved.

Evidence from in vitro studies and animal models

*In vitro* experiments provide the evidence that strontium ranelate is able to directly inhibit the recruitment and activity of osteoclasts. Strontium ranelate significantly and dose-dependently inhibited the expression of two osteoclast markers: carbonic anhydrase-II and the \( \alpha \) subunit of the vitronectin receptor in a chicken bone marrow culture system, suggesting that this agent has an inhibitory effect on the differentiation of pre-osteoclasts into osteoclasts [25]. The dose-dependent inhibitory effect of strontium ranelate on the resorbing activity of osteoclasts was further demonstrated using a pit assay of isolated rat osteoclasts [25], the pit area resorbed by isolated mouse bone marrow osteoclasts in dentine slices and the \( ^{45}\text{Ca} \) release from organ cultures of mouse fetal long bones under basal or 1,25(OH)\( _2 \)D\( _3 \)-stimulated conditions [26]. Strontium ranelate was also shown to decrease osteoclast resorbing activity, increase apoptosis of isolated rabbit osteoclasts [27] and to reduce human peripheral blood monocyte differentiation into osteoclasts [28]. Strontium ranelate was shown to increase the recruitment and activity of osteoblastic cells using \( ^{3} \text{H}\)-thymidine- and \( ^{3} \text{H}\)-proline-labelled calvariae of newborn rats [29]. Treatment with strontium ranelate also significantly increased osteoblastic proliferation/replication 3- to 4-fold as evaluated by the measurement of DNA synthesis in cell populations enriched with fibroblasts or pre-osteoblastic cells [29]. In an osteogenic model of differentiating mouse calvaria-derived osteoblastic cells, strontium ranelate increased alkaline phosphatase activity (a marker of osteoblast differentiation) and increased collagen synthesis without affecting matrix mineralization [30]. Strontium ranelate was shown to stimulate osteoblastic differentiation by the induction of gene expression of the master gene *Runx*\( _2 \) and bone sialoprotein that was associated with a significant increase in the formation of colony-forming unit osteoblasts [31], and also significantly increased human primary osteoblast survival under oxidative stress conditions [32]. Studies in primary human osteoblasts suggest that strontium ranelate may also have the ability to promote the differentiation and survival of osteocytes, an additional mechanism potentially contributing to its anti-fracture efficacy [33]. More recently, *in vitro* assays on primary murine bone cells confirmed the dual mode of action of strontium ranelate by providing evidence for stimulation of bone formation through a positive action on osteoblast differentiation and action and a decrease in osteoclast differentiation and function by disrupting actin cytoskeleton organization [34].

Data from animal models

Two models were used to investigate the effects of strontium ranelate in the prevention of bone loss in osteopenic animals. Administration of strontium ranelate for 2 months to rats immediately after ovariectomy prevented trabecular bone loss. The biochemical and histological changes observed showed that strontium ranelate acted as an uncoupling agent, preventing the increased bone resorption associated with oestrogen deficiency while maintaining high levels of bone formation, thus dissociating the two components of bone remodelling. A decrease in osteoclast surface and number was observed in treated animals, and bone volume was 30% greater than in untreated controls [35]. Treatment with strontium ranelate was also associated with an improvement in bone microarchitecture and bone strength [36]. In rats with hind limb immobilization, strontium ranelate increased alkaline phosphatase activity without altering bone mineralization, was only partially able to prevent the bone loss induced by immobilization [37].

Potential molecular mechanisms by which strontium ranelate exerts its dual action

At least two putative molecular targets have been suggested for the actions of strontium ranelate on bone cells: the calcium sensing receptor (CaSR) or another cation-sensing receptor, and the RANK/RANK ligand (RANKL)/osteoprotegerin (OPG) signalling pathway [38] (Fig. 1).

CaSR (or another cation-sensing receptor)

The CaSR is a G protein-coupled receptor that was first cloned from parathyroid cells and subsequently found to be expressed in many other tissues, including osteoblasts and osteoclasts [39]. Strontium, a divalent cation closely resembling Ca\( ^{2+} \) in its atomic and ionic properties, is an agonist of the extracellular CaSR [40]. Studies in rat primary osteoblasts, obtained from calvarial cultures expressing the CaSR endogenously, demonstrate that strontium is a full CaSR agonist and that strontium ranelate enhances osteoblast proliferation and bone formation via a CaSR-mediated effect [41]. CaSR activation is thus at least in part responsible for mediating the anabolic actions of Sr\( ^{2+} \) on bone [41, 42]. However, studies in mice with targeted disruption of the CaSR gene (CaSR-null mice) support the additional involvement of another cation-sensing mechanism, distinct from CaSR, in activating osteoblast replication [43]. The CaSR has also been shown to be involved in strontium ranelate-induced osteoclast apoptosis [44].

The RANK/RANKL/OPG pathway

The concerted actions of OPG, RANK, and its ligand, RANKL, play a central role in maintaining the delicate balance between bone resorption and formation, and in the preservation of bone mass [45–47]. *In vitro* data suggest that after 24-h incubation, strontium ranelate enhances OPG expression while simultaneously down-regulating RANKL expression in primary human osteoblastic cells, the combined effect of which leads to decreased osteoclastogenesis [33]. These data suggest that the RANK/RANKL/OPG pathway is a key molecular target for the dual mode of action of strontium ranelate on bone cells.

Effects of strontium ranelate on bone strength

Data from intact animal models

In normal adult mice, strontium ranelate increased trabecular bone volume dose-dependently, as evaluated by histomorphometry of the vertebrae [48]. In normal rats treated with strontium ranelate, an increase in the diameter of the humeral shaft was observed, suggesting an effect on periosteal bone formation [49]. An increase in trabecular thickness and number and a decrease in trabecular separation were also observed in the axial and appendicular skeleton [49]. In monkeys treated with strontium ranelate for 52 weeks, there was a dose-dependent uptake of the compound into cortical and cancellous bone, with a 1.6-fold higher content in new than in old bone. Strontium uptake into bone decreased by 50% 10 weeks after treatment withdrawal, and this was almost exclusively in new bone. Crystal characteristics of bone mineral were preserved at the end of treatment, confirming that strontium ranelate was
only weakly linked to crystals and did not affect bone mineralization, as mean degree of mineralization was preserved [50].

Beside its influence on determinants of bone strength such as geometry and microarchitecture, which is likely to be related to a cellular effect, strontium ranelate was also shown to increase elastic modulus, hardness and dissipated energy in rat vertebrae, using the technique of nanoindentation. These changes in intrinsic bone tissue quality may contribute to the increase in bone strength and decreased fracture risk observed in strontium ranelate-treated osteoporotic patients [51].

Studies on intact animals confirm that strontium ranelate improves bone microarchitecture at both trabecular and cortical levels and preserves the structure of bone matrix crystals without affecting the mineralization process. It is possible that these changes may be associated with an improvement in the biomechanical properties of bone.

Data from an ovariectomized rat model

In an ovariectomized rat model, strontium ranelate was shown to improve bone strength by preventing ovariectomy-induced vertebral biomechanical degradation, thereby positively influencing bone resistance determinants. Prevention of ovariectomy-induced bone loss and microarchitectural degradation was associated with a beneficial effect on intrinsic bone material quality [52].

Clinical evidence for the effects of strontium ranelate on bone strength

Effects on BMD

Strontium ranelate has been shown to significantly increase BMD at the lumbar spine, femoral neck and total hip. Whereas overestimation of BMD should be taken into consideration due to skeletal accretion of strontium in strontium ranelate-treated patients [53, 54], BMD changes have nevertheless been shown to be significantly related to fracture risk reduction. A post hoc analysis of pooled data from the SOTI and TROPOS studies thus demonstrated that changes of BMD at the femoral neck after 3 years of treatment were predictive of vertebral fracture risk reduction, with each 1% increase in femoral neck BMD found to be associated with a 3% reduction in vertebral fracture risk. Changes in BMD thus explained 76% of the fracture risk reduction observed after 3 years of treatment [55]. An increase in femoral neck BMD after 1 year of treatment was also associated with a reduction in new vertebral fractures after 3 years of treatment ($P=0.04$). During 3 years of treatment, femoral neck BMD changes were also associated with hip fracture risk reduction [56]. These data suggest that femoral neck BMD assessment may be a more appropriate monitoring tool than lumbar spine BMD measurements in strontium ranelate-treated patients.

Effects on bone microarchitecture in patients treated with strontium ranelate

Forty-one unpaired bone biopsies obtained from patients participating in the SOTI and TROPOS studies were examined using 3D micro-CT (µCT) [24]. Compared with placebo ($n=21$), strontium ranelate-treated biopsies ($n=20$) demonstrated a significant increase in the number of trabeculae (+14%; $P=0.05$), decrease in trabecular separation (−16%; $P=0.04$) and increase in cortical thickness (+18%; $P=0.008$). There was also a shift in trabecular structure from rod-like to plate-like configuration resulting in an improved trabecular structural model index and substantially stronger bone in strontium ranelate-treated compared with untreated patients (−22%; $P=0.01$) [24] (Fig. 2). These changes in trabecular and cortical microstructure are likely to improve the biomechanical properties of bone and contribute to the anti-fracture efficacy observed with strontium ranelate.

Conclusion

Increasing knowledge about the cellular and molecular pathways involved in the maintenance of bone homeostasis and about the role of disturbances in these pathways in the pathogenesis of osteoporosis has paved the way for a better understanding of the putative mechanisms responsible for the beneficial effects of strontium ranelate on bone. A decade of extensive in vitro and in vivo pre-clinical evaluation followed by a comprehensive clinical
programme in postmenopausal women has led to the realization that strontium ranelate represents a novel and unique approach in the management of osteoporosis by its ability to restore the imbalance between bone resorption and formation in favour of bone formation and by its beneficial effects on bone micro-architecture, which improve the biomechanical properties of bone.

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