

## PERSPECTIVES

### Bone Quality and Strontium Ranelate

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#### Abstract

Given its increasing incidence and serious complications, osteoporosis requires safe and effective long-term treatment. Strontium ranelate is an osteoporosis treatment with a broad spectrum of safety and efficacy in reducing the risks of both vertebral and nonvertebral (including hip) fractures in a wide variety of patients. This treatment should be considered as a first-line option to treat women at risk of osteoporotic fractures, whatever their age, the severity of the disease and their risk factors. The analysis of transiliac bone biopsies has provided further evidence of the good bone tissue safety of strontium ranelate. Results are fully consistent with the mode of action of strontium ranelate involving dissociation between bone formation and bone resorption. Strontium ranelate treatment appears to stimulate both trabecular and cortical bone formation in 3D analyses, but without increasing cortical porosity. The change in 3D trabecular and cortical microarchitecture may improve bone biomechanical competence and explain the decreased fracture rate after treatment. We now have evidence that strontium (Sr) is heterogeneously distributed in bone tissue and is exclusively present in bone formed after the beginning of treatment. Sr is absent from old bone formed before treatment, but focal bone Sr content is constant during treatment. Whatever the duration of treatment and the content of Sr in bone, the variables reflecting secondary mineralization at the tissue level are maintained at normal levels. However, the influence of Sr on the quality of bone mineral and its mineralization remains to be clarified. *IBMS BoneKEy*. 2010 March;7(3):103-107.

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Strontium ranelate (Protelos<sup>®</sup>, 2 g/day) is an effective and well-tolerated treatment for postmenopausal osteoporosis. It provides early and sustained vertebral and nonvertebral (including hip) antifracture efficacy and increases bone mineral density (BMD) at the spine and femur (1;2). These observations reported at the end of phase III studies (3 years of treatment) have now been demonstrated over 5 years in an extension of the randomized trial years (3) and over 8 years in an open-label phase of the extension of phase III studies (4;5). Some bone biopsies have been obtained from the extension studies. Thus, long-term treatment with strontium ranelate in postmenopausal osteoporotic women leads to continued increases in BMD at all sites, and provides some evidence for sustained antifracture efficacy (3-5). Bone quality is influenced by different extrinsic determinants (mass, size, geometry, and microarchitecture), but also by the intrinsic material properties of the tissue (mineralization, organic matrix

characteristics, accumulation of microdamages, and apoptosis of osteocytes).

*In vitro* studies suggest that strontium ranelate potentially increases the bone formation activity of osteoblasts and decreases the bone resorption activity of osteoclasts, thus leading to the prevention of bone loss and an increase in bone mass and strength in animals (6) and in humans (1). In monkeys (7;8), strontium (Sr) induced no significant change in mineral at the crystal level and was heterogeneously distributed in bone with more Sr in recent bone formed during the administration of strontium ranelate than in old bone. Previous observations (9-11) have shown that Sr ions were present at the mineral substance level following either ionic exchanges onto the area of crystals, or ionic substitution with calcium ions within the crystal lattice of apatite of newly-formed mineral. No defect of mineralization due to strontium ranelate was observed in studies

on animals (7;8;12;13) and humans (14-18) at the tissue and crystal levels (no osteomalacia, no modification of the mineralization mechanism, and no change in the size of crystals), even at dosages much higher than the therapeutic dosage for osteoporosis. The positive effects of strontium ranelate on bone formation were confirmed by augmented mineral apposition rate and osteoblast surfaces (14). Strontium ranelate improved bone strength and the determinants of bone resistance in animals (19).

Recent observations in postmenopausal osteoporotic women treated for 2 and 3 years with strontium ranelate confirmed the heterogeneous distribution of Sr in bone (16). Sr was dose-dependently deposited in bone, with an almost exclusive content found in newly-formed bone structural units (BSUs), as compared to old BSUs that were almost constantly devoid of Sr even after 3

years of treatment (Fig. 1) (16). At the therapeutic dosage of 2 g/day, bone Sr content at the tissue level was only slightly higher after 3 years of treatment than after 2 years, confirming chemical analyses showing that a plateau was reached after 2 and 3 years of treatment (16). In new BSUs containing Sr, Sr content was also similar after 2 and 3 years of treatment. The exclusive presence of Sr in new bone suggested that Sr was mainly exchanged onto the crystal surface rather than deeply and durably substituted for calcium ions. Such a situation also favors a rapid clearance of Sr from bone, already described in monkeys (7;8) but not yet studied in women. The degree of mineralization of bone measured with microradiography (16) was not different in patients treated with either strontium ranelate or placebo regardless of the dose (0.5 to 2 g/day) or of the duration of the treatment (2 or 3 years).

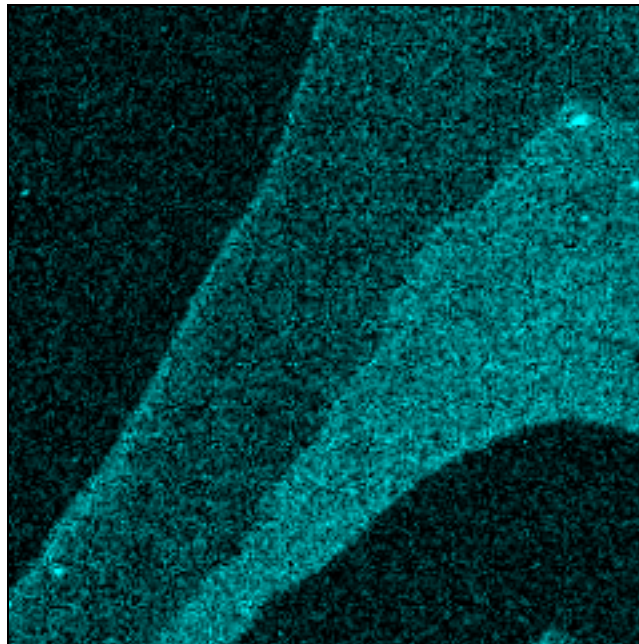


Fig. 1. An iliac bone sample from a postmenopausal osteoporotic woman treated with strontium ranelate (2 g/day for 3 years). X-ray microanalysis illustrates the distribution of strontium in a recent BSU from trabecular bone. Old bone tissue formed before the beginning of treatment does not contain strontium.

Recently, the potential impact of Sr on human bone material quality was investigated in a small number of transiliac bone biopsies from postmenopausal osteoporotic women treated for 3 years with

strontium ranelate or placebo (17). Bone mineralization density distribution (BMDD, a variable reflecting the content of calcium in bone tissue and thus close to the degree of mineralization), Sr concentration, the

collagen cross-link ratio and the indentation modulus were analyzed by quantitative backscattered electron imaging, electron-induced X-ray fluorescence analysis, synchrotron radiation-induced micro X-ray fluorescence elemental mapping, Fourier transform infrared imaging and nanoindentation, respectively. BMDD in strontium ranelate-treated patients was shifted to higher atomic numbers compared to the placebo, suggesting a small increase of BMD. Sr was preferentially incorporated in bone packets formed during treatment. The collagen cross-link ratio was preserved in treated bone. The indentation modulus was significantly decreased in younger versus older bone packets for treated individuals, revealing a link between indentation modulus and bone mineralization as shown previously in normal bone tissue (20;21). In bone material prepared similarly (dry samples), strontium ranelate treatment does not compromise mechanical properties at the tissue level (12;17). Altogether, these findings confirmed a previous finding (16) indicating that after strontium ranelate treatment, Sr was heterogeneously distributed in bone and preferentially present in bone packets formed during treatment. Taken together, these data provide evidence that the investigated bone quality determinants at the tissue level were unchanged in postmenopausal osteoporotic women treated with strontium ranelate.

These data have now been extended by the study of iliac bone samples taken from postmenopausal osteoporotic women after 2 months, and 1 to 5 years of treatment with strontium ranelate (22). The major results can be summarized as follows: 1) Sr is heterogeneously distributed in bone tissue and is exclusively present in bone formed after the beginning of treatment; 2) bone Sr distribution increases mainly during the first 3 years of treatment and then slows down; 3) the extent of areas containing Sr, illustrating the activity of formation during strontium ranelate treatment, is often higher in cancellous than in cortical bone; 4) strontium is absent from old bone formed before treatment, but Sr focal content in new bone is constant during treatment and is

similar in recently-formed cortical and cancellous bone tissue; and 5) whatever the duration of treatment and the content of Sr in bone, the variables reflecting secondary mineralization at the tissue level are maintained in a normal range.

A recent study has investigated, in a very small number of bone samples, the potential influence of strontium ranelate treatment (2 g/day for 3 years versus placebo) on human bone tissue characteristics and quality at the micro- and nanostructural levels (18). Synchrotron radiation with a microbeam, combining scanning small-angle scattering, X-ray diffraction and fluorescence spectroscopy, were used for a detailed characterization of mineral crystals within the collagenous bone matrix. A scanning procedure allowed the simultaneous determination of maps of chemical composition together with thickness, length and lattice spacing of mineral crystals within a thin bone section. Fluorescence results confirmed again that only bone packets or osteons formed during strontium ranelate treatment contain significant amounts of Sr and that up to 0.5 out of 10 calcium atoms in the mineral crystals are replaced by Sr, as revealed by a corresponding shift in apatite lattice spacing. Similar results had been reported previously in monkeys (7;8). The thickness and length of plate-shaped bone mineral crystals were not affected by strontium ranelate treatment. Thus, there was no indication for a change in human bone tissue quality at the nanoscale after a 3-year treatment of postmenopausal osteoporotic women with strontium ranelate.

In conclusion, all the recent data obtained in postmenopausal osteoporotic women after 3 years of treatment with strontium ranelate show that the quality of bone mineralization is preserved at a normal level and that this is maintained after prolonged treatment (up to 5 years). With strontium always being localized in bone tissue that is recently formed, i.e., with a low degree of mineralization, the global bone density measured at the tissue level was normal and neither increased nor decreased. Finally, the effects of strontium ranelate treatment on fracture prevention also depend on other

determinants, such as an improvement of bone microarchitecture (14).

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