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Strontium ranelate – a promising therapeutic principle in osteoporosis

Georges Boivin[a,b,*], Audrey Doublier[a,b], Delphine Farlay[a,b]

[a] INSERM, UMR 1033, F-69372 Lyon, France
[b] Université de Lyon, F-69008 Lyon, France

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ABSTRACT

Strontium ranelate (2 g/day) appears to be a safe and efficient treatment of osteoporosis (OP), reducing the risks of both vertebral and non-vertebral fractures (including hip) in a wide variety of patients. Thus, the agent can now be considered as a first-line option to treat women at risk of OP fractures, whatever their age and the severity of the disease. A long-term treatment with strontium ranelate in OP women leads to a continued increase in bone mineral density at spine and hip levels, and a sustained antifracture efficacy. The mode of action of strontium ranelate involves a dissociation between bone resorption and formation, as the bone formation rate is increased and not influenced by the antiresorptive action of the agent. Strontium is heterogeneously distributed in bone tissue: it is absent from old bone tissue and is exclusively present in bone formed during the treatment. Total area containing strontium in bone tissue increases during treatment, although the focal bone strontium content is constant. Whatever the duration of treatment and the content of strontium in bone, the degree of mineralization is maintained in a normal range. Furthermore, no change at crystal level is detected up to 3 years of treatment.

Introduction

Strontium ranelate (2 g/day) is now considered as an effective anti-osteoporotic drug developed for the treatment of postmenopausal osteoporosis. *In vitro* and *in vivo* experimental studies [1–9] have demonstrated that strontium ranelate has a dissociating effect on bone remodeling by maintaining bone formation and decreasing bone resorption, resulting in an increase in bone mass and strength [9–13]. In clinical studies, strontium provides early and sustained vertebral and non-vertebral (including hip) antifracture efficacy, and increases the bone mineral density at the spine and hip levels [14–18]. Human studies also show an improvement of microarchitecture under strontium ranelate treatment [19–21]. Upon studying the mechanisms of action of agents that reduce the risk of low-energy fractures, it is necessary to disclose their influence on bone mineralization, one of the major parameters reflecting bone quality [22].

Mineralization is known to vary over microscopic regions, with age of the bone structural units (BSU), the recently deposited ones being much less calcified than the older ones (Fig. 1). During bone remodeling, after the resorption, bone formation is a multi-step process. Following its deposition, the new matrix begins to mineralize after about 5–10 days from the time of deposition and the linear rate of this *primary mineralization* can be measured directly *in vivo* using double tetracycline labelling. After full completion of the BSU (osteons in cortical bone or cancellous packets) a *secondary mineralization* begins. The secondary mineralization progressively augments the mineral content of bone matrix [23–25]. This process consists of an increase in the number of crystals, a maturation of the mineral components, and an increase of the perfection of crystal unit cells [23,26–29]. The heterogeneity of the mineralization is slightly higher in cortical bone than in trabecular bone. In human control bone the heterogeneity does not vary with sex and age [23,27].

Bone mineralization influences the mechanical strength of bone tissue [30,31] and its contribution to bone microhardness is well known [27]. The heterogeneity index of mineralization also influences bone strength, as a homogenization of the mineralization may make the bone tissue more brittle [26]. The level of secondary mineralization appears to be a major cause of change in the microhardness of bone tissue, although microhardness is also influenced by the organic matrix [27,32]. The present survey discusses the mode of action of strontium ranelate on bone mineralization as compared to other agents used in the treatment of osteoporosis.

Effect of accelerated bone formation on mineralization

In adult bone, the major biological determinant of mineralization is the rate of remodeling. Accelerated bone formation is physiologically accompanied by accelerated resorption, involving an augmentation of the remodeling rate which decreases the

* Corresponding author at: INSERM Unité 1033, Université de Lyon, Faculté de Médecine Lyon Est (domaine Laennec), 69372 Lyon Cedex 08, France.
E-mail address: georges.boivin@univ-lyon1.fr (G. Boivin).

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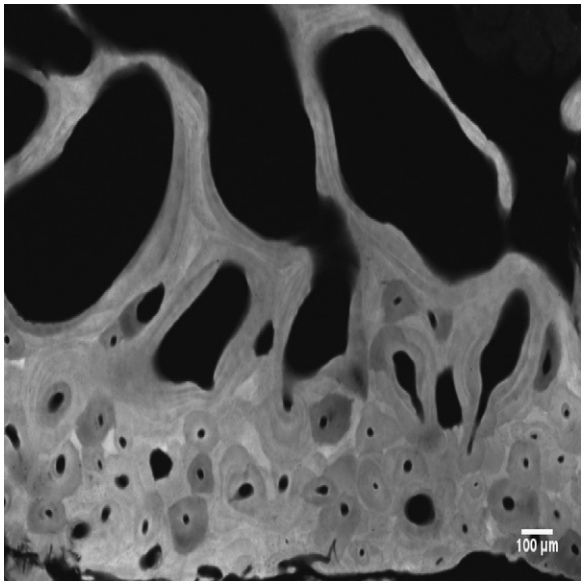

Fig. 1. Microradiograph illustrating the heterogeneity of the secondary mineralization from an osteoporotic woman treated with 2 g/day of strontium ranelate for 36 months. The more the bone tissue is dark grey the less it is mineralized, and conversely.

"lifespan" of BSU, *i.e.*, of the time available for the secondary mineralization. This leads to the fact that new BSU are eroded before they have fully completed their secondary mineralization, as proven by the presence of a large amount of BSU that are not completely mineralized and a low mean degree of mineralization [23,24,27].

In eleven cases of typical primary hyperparathyroidism with hypercalcemia and renal calculi, the degree of mineralization of bone is significantly ($p < 0.05$) lower (0.90 ± 0.07 g/cm^3) than in control patients of the same age (1.09 ± 0.08 g/cm^3). The heterogeneity index is however not significantly modified (0.25 ± 0.07 g/cm^3), which is in line with the shift towards low values of the distribution of mineralization. In osteoporotic women treated with teriparatide, a recombinant form of parathyroid hormone, the results are similar with a decrease of the degree of mineralization and a small increase of the heterogeneity index [33,34].

Effect of reduced rate of bone resorption on mineralization

A marked reduction in the "birthrate" of bone remodeling units following the use of antiresorptive agents such as bisphosphonates, estrogens or SERMs, prolongs the "lifespan" of the BSU, allowing a more complete secondary mineralization [35–38]. The latter leads to an increase in the degree of mineralization of bone, explaining in great part the increase of bone mineral density at the organ level, and the improvement of biomechanical characteristic such as hardness. The deep decrease of the remodeling activity not only affects the degree of mineralization but also the heterogeneity index of mineralization. In osteoporotic women treated with alendronate for 2–3 years, the degree of mineralization is augmented by 7–11% and the heterogeneity index decreases. If such a trend is confirmed after long-term treatments (>5 years), this might be detrimental to the quality of bone tissue and its biomechanical properties, as a homogenization of the bone mineralization may lead to brittle bone tissue. A substantial retardation of the bone remodeling may prevent the microcracks removal, and thus lead to bone fracture [22].

The possible adverse effects of long-term alendronate therapy on intrinsic bone properties have been recently studied among 32 outpatient clinic post-menopausal osteoporotic women treated with oral alendronate (ALN) for a mean of 6.4 ± 2.0 years. [39]. Increased degree of mineralization associated with lower crystallinity and microhardness in long-term-treated women suggests an alteration of the quality of bone matrix. These effects were studied on iliac cortical bone to assess the mineral and collagen quality and the micromechanical properties, independently by design of the degree of mineralization [40]. The deficits in strength are in part related to difference in crystallinity, irrespective of the mineral amount, its maturity but also of the collagen maturity. These original findings at local levels of bone structure will have to be taken into account in the study of pathophysiology of bone fragilities associated with prolonged treatment with bisphosphonates.

Bone mineralization and strontium ranelate

Strontium ranelate has a dissociating effect on bone remodeling by maintaining bone formation and decreasing bone resorption, leading to prevention of bone loss and increase in bone mass and strength in rats [41]. Studies in monkeys [42,43] as well as observations in post-menopausal osteoporotic women treated for 3 years with strontium ranelate (2 g/day) [15,18,44], allowed to evaluate: (1) the relative calcium, phosphorus and strontium bone contents, (2) the distribution of strontium in cortical and cancellous bone, (3) the interactions between strontium and mineral at crystal level, (4) the influence of strontium on the degree of mineralization of bone and, (5) the bone clearance of strontium over short periods of time after cessation of administration. In treated women, strontium is deposited in newly formed BSU mineralized during the therapeutic period. Whatever the bone strontium content and the duration of treatment, the variables reflecting the secondary mineralization of bone (degree of mineralization and heterogeneity index) are maintained at values (1.12 ± 0.09 and 0.26 ± 0.07 g/cm^3, respectively) situated in a physiological range. These data suggest that the increased bone mineral density at organ level observed during strontium ranelate treatment could be due, at least in part to an improvement of bone microarchitecture, leading to improved biomechanical properties [45,46].

A recent study in post-menopausal osteoporotic women treated for 3 years with strontium ranelate, shows that strontium was exclusively present in bone formed during treatment, and was heterogeneously distributed with higher focal concentrations in bone formed during treatment than in old bone formed before the beginning of treatment [44]. The X-ray cartography, illustrating the extent of bone areas containing strontium and thus the formation activity of strontium during treatment, shows an increase of bone areas containing strontium until 3 years, often higher in cancellous than in cortical bone [44]. Secondary mineralization is maintained at a normal level during the treatment [44]. These observations confirmed the previous ones in monkeys receiving strontium ranelate for 13 weeks [42] and 52 weeks [43]. Moreover, the incorporation of strontium within the apatite crystals represents a maximum of 1 strontium ion per 10 calcium ions in monkeys [42,43] and a maximum of 0.5 strontium ion in women treated for 3 years [47].

We have recently shown that even after a long-term treatment (up to 5 years) and whatever the distribution of strontium in bone, the quality of bone mineralization (degree of mineralization and heterogeneity index) is maintained at tissue level [48]. The potential effect of strontium on bone apatite crystals has been finally investigated in paired biopsies of osteoporotic women treated for 3 years with either strontium ranelate or a placebo [Doublier et al. in preparation]. Parameters reflecting crystal and unit cell characteristics (crystallinity, apparent length and width/thickness of crystals, interplanar distances and lattice parameters of unit cells) are not influenced by the presence of strontium and were