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REVIEW

Strontium ranelate: A novel mode of action leading to renewed bone quality

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Abstract Various bone resorption inhibitors and bone stimulators have been shown to decrease the risk of osteoporotic fractures. However, there is still a need for agents promoting bone formation by inducing positive uncoupling between bone formation and bone resorption. In vitro studies have suggested that strontium ranelate enhances osteoblast cell replication and activity. Simultaneously, strontium ranelate dose-dependently inhibits osteoclast activity. In vivo studies indicate that strontium ranelate stimulates bone formation and inhibits bone resorption and prevents bone loss and/or promotes bone gain. This positive uncoupling between bone formation and bone resorption results in bone gain and improvement in bone geometry and microarchitecture, without affecting the intrinsic bone tissue quality. Thus, all the determinants of bone strength are positively influenced. In conclusion, strontium ranelate, a new treatment of postmenopausal osteoporosis, acts through an innovative mode of action, both stimulating bone formation and inhibiting bone resorption, resulting in the rebalancing of bone turnover in favor of bone formation. Strontium ranelate increases bone mass while preserving the bone mineralization process, resulting in improvement in bone strength and bone quality.

Keywords Bone quality · Strontium ranelate

Introduction

Various bone resorption inhibitors and bone stimulators have been shown to decrease the risk of osteoporotic fractures. However, there is still a need for agents promoting bone formation by inducing positive uncoupling between bone formation and bone resorption. Strontium ranelate (Protelos) simultaneously increases bone formation and decreases bone resorption, resulting in the rebalancing of bone turnover in favor of bone formation. This unique mode of action leads to positive effects on bone strength and its determinants and could certainly explain the clinical effects of strontium ranelate. It has recently been demonstrated that it reduces both vertebral and hip fracture risk and so is a good candidate [1, 2].

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Bone strength and its determinants

The aim of any anti-osteoporotic treatment is to improve bone strength and thus to decrease the risk of fracture [3–5]. In humans, the approach to evaluating bone strength is the recording of the fracture rate, which implies a large group of patients. Thus, a fracture is not only due to decreased bone mineral mass or alteration in the microarchitecture but is also related to falls, as a result of loss of balance, inappropriate protective responses, or muscle weakness [3–5]. Careful and specific investigation in animal models of treatments against osteoporosis with regard to bone strength and its determinants is therefore of major importance.

Bone strength is determined by bone geometry, cortical thickness and porosity, trabecular bone morphology, and intrinsic properties of bone tissue. Bone strength is indirectly estimated by bone mineral density (BMD) using dual energy X-ray absorptiometry (DXA). Since DXA-based BMD accounts for 60–70% of the variation in bone strength, some important factors are not captured by DXA in the progression of osteoporosis and the effects of anti-osteoporotic treatment. Geometry and trabecular microarchitecture have also to be taken into account. Thus, the assessment of intrinsic mechanical quality of bone tissue should provide better understanding of the role of tissue quality in determining bone strength.

More recently, a nanoindentation technique has been applied to investigate tissue quality by measuring both hardness and elasticity of dry and wet bone tissue with a high spatial resolution [6, 7]. Nanoindentation consists of compressing a pyramidal diamond tip into a material and simultaneously recording force and displacement with μN and nm resolution. From the resulting force-displacement curves, hardness, the maximal force per unit area, dissipated energy, and indentation modulus—a purely elastic property—can be calculated. The nanoindentation method allows the mechanical properties of single bone structural units to be quantified. Few results are currently available, but local elastic properties of bone structural units have been found to vary significantly among individuals and anatomical locations [7–11]. Little correlation was found between age and the elastic properties of bone tissue [9, 10]. Nanoindentation could represent a tool of major importance for evaluating the tissue quality and for better understanding of the mechanism by which treatments of osteoporosis could improve bone strength. In the future, this could help to investigate, on bone biopsy, the contribution of tissue quality in the determination of bone fragility.

The careful investigation of all of these determinants of bone strength (bone tissue included) should be considered in the pathophysiology of osteoporosis and in the mechanisms of action of anti-osteoporotic drugs.

Effects of inhibitors of bone resorption on bone strength and its determinants

Most of the clinical studies on inhibitors of bone resorption like estrogen, selective estrogen receptor modulators (SERMs), or bisphosphonates have shown an association between the increment in areal BMD and the decreased risk of fracture, but the modifications are not always commensurate [12–14]. Indeed, while BMD seems to be a good predictor of bone strength, it could be confusing in certain conditions of treatment. Raloxifene and alendronate treatment are both associated with a reduction in vertebral fracture close to 50%, but the effect on BMD of treatment with raloxifene (+3%) is less pronounced than that of treatment with alendronate (+8%) [12, 15–17]. In a recently reported animal study [18], the administration of inhibitors of bone resorption (SERMs or bisphosphonate) restored the mechanical resistance and the areal mineral density after ovariectomy, but did not correct cancellous bone mass. These agents, by differently modulating bone turnover through different mechanisms, could increase the intrinsic properties of bone and cancellous bone architecture rather than the cancellous bone mass. These findings thus imply that not only bone quantity but also intrinsic properties of bone and cancellous architecture play an important role in the mechanical resistance to fracture [18].

One parameter, which should also be considered, is the degree of mineralization. Increased bone strength is observed on bisphosphonate therapy, without significant modification of bone mass or trabecular volume as evaluated by histomorphometry [19–21]. A more homogeneous degree of mineralization is observed, which could account for the increment in BMD and bone strength. The rate of bone remodeling could also be implicated. Clinical studies indicate that markers of bone remodeling could be independent predictors of the risk of fracture [22]. By different distribution of stress in relation to the volume of bone in a phase of remodeling, a high remodeling rate could jeopardize mechanical strength. Alternatively, decreased bone remodeling could influence trabecular bone geometry and the degree of mineralization of the matrix formed on treatment.

Effects of stimulators of bone formation on bone strength and its determinants

Fluoride treatment induced a major increase in BMD (+10%/year) but did not reduce the incidence of fracture [23–29]. Overall analysis of the current preclinical studies indicates that fluoride does not improve bone strength in several animal models including rats, minipigs, and rabbits, although it can increase spinal bone mass as in humans, at least in the so-called "good responders." Several possible explanations have been proposed for the discrepancy, among them the severity of osteoporosis at the beginning of treatment, the absolute daily doses, the dosing schedule, and the duration of treatment. Thus, the quality of the crystal obtained on fluoride treatment might also be responsible for this poor effect on bone strength despite a positive effect on bone mass.

Other stimulators of bone formation [30–40] such as insulin-like growth factor 1 (IGF-I), growth hormone, or parathyroid hormone (PTH) stimulate the periosteal apposition and increase the external diameter of long bones. This expansion of the outer diameter of long bone is associated with a marked increase in bone strength. When associated with an inhibitor of bone resorption, an increase in cortical thickness can also be observed and corresponds to an inhibition of endosteal bone resorption [31, 32], thereby participating in the improvement in bone strength. An expansion of bone diameter could also be observed in humans. Thus, during growth, bone diameter is influenced by the nutritional environment, as for example by calcium/phosphate salt supplements [41].

On PTH treatment, an increased bone area can even be detected. An excess of growth hormone, as in acromegaly, increases bone size. Thus, an expansion of bone size is possible in adults, but the specific role of this modification in the risk of fracture remains to be established. These modifications of bone mass and size also resulted in a major increase in BMD and improvement in microarchitecture.

Effect of the innovative agent strontium ranelate on bone strength and its determinants

In vitro studies have suggested that strontium ranelate enhances osteoblast cell replication and activity [42]. Simultaneously, strontium ranelate dose-dependently inhibits osteoclast activity [43, 44]. In vivo studies in various rodent models like intact animals, model of immobilization, or ovariectomy-induced osteoporosis, suggest the same effects: strontium ranelate stimulates bone formation and inhibits bone resorption in mice and rats [45–49] and prevents bone loss and/or promotes bone gain, as investigated by histomorphometry, DXA, and biomechanics [50].

In intact female rats, a 2-year period of exposure to strontium ranelate mixed in the diet induced a dose-dependent increase in bone mechanical properties at the level of the vertebral body, which contains a large proportion of trabecular bone, and at the level of the mid-shaft femur, which mainly contains cortical bone [50]. The increase in bone strength was related to a dose-dependent increase in bone mass and bone volume and can also be due to an improvement in bone tissue quality. The increase in trabecular bone volume, trabecular number, trabecular thickness, and cortical thickness, as assessed at the tibia level by histomorphometry, is in agreement with a net gain in bone tissue mass. Strontium ranelate improves bone geometry by increasing external diameter and cortical thickness of the long bone through periosteal apposition.

The increment in bone mechanical properties was characterized by an increase in ultimate strength but also by a dramatic improvement in energy to failure, which was essentially due to an increment in plastic energy. Such modifications observed on strontium ranelate treatment are in good agreement with an improvement in intrinsic bone quality and also in trabecular bone mass, leading to greater bone resistance. These results strongly suggest that new bone formed following strontium ranelate treatment is able to withstand greater deformation before fracture, while possessing similar elastic properties to normal bone. Furthermore, a 2-year exposure to strontium ranelate did not cause any alteration in bone mineralization, as assessed by histomorphometry, or bone stiffness. Recent data indicate that intrinsic bone tissue quality in rats treated lifelong with strontium ranelate was similar to that of intact rats of the same age [51]. The same results are obtained at the level of mineralization, which is not affected by bone balance and bone mass. It has been shown that the distribution of strontium ranelate in bone is dependent on the dose, the duration of exposure, gender, and skeletal site. Strontium is distributed in calcified matrix and is easily exchangeable from bone mineral, being slightly linked to mature crystals through ionic substitutions. Strontium is heterogeneously distributed in bone with a higher concentration in new than in old bone, in both trabecular bone and cortical bone [52].

This positive uncoupling between bone formation and bone resorption results in bone gain and improvement in bone geometry and microarchitecture and, consequently, improvement in bone strength. These observations in animals fully predict what is observed in postmenopausal women. Indeed, strontium ranelate treatment stimulates bone formation and decreases bone resorption in postmenopausal osteoporotic women, resulting in a decrease in vertebral and hip fracture rates [1, 2]. Thus, strontium ranelate is the first anti-osteoporotic agent combining both a stimulation of bone formation and an inhibition of bone resorption for an optimal effect on all the determinants of bone strength.

Conclusion

Strontium ranelate, a new treatment of postmenopausal osteoporosis, acts through an innovative mode of action, both stimulating bone formation and inhibiting bone resorption, resulting in a rebalancing of bone turnover in favor of bone formation.

Strontium ranelate increases bone mass while preserving the bone mineralization process, resulting in improvement in bone strength and bone quality.

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