

Improvement in bone strength parameters. The role of strontium ranelate

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Abstract

Strontium ranelate (SR) is a novel anti-osteoporotic agent approved for the treatment of postmenopausal osteoporosis. SR appears to reduce bone resorption by decreasing osteoclast differentiation and activity, and to stimulate bone formation by increasing replication of pre-osteoblast cells, leading to increased matrix synthesis. The effect of SR on bone strength indices has been investigated in several animal models, including intact female and male rats, ovariectomized rats, after rat limb immobilization and in monkeys. In intact female rats, SR significantly improved bone mechanical properties of vertebrae and midshaft femur. The improvement in bone mechanical properties was characterized by an increase in maximal load and in energy to failure, which was due to an increment in plastic energy. These results suggest that new bone formed following strontium ranelate treatment is able to withstand greater deformation before fracture. Moreover, in ovariectomized rats, a model that resembles postmenopausal osteoporosis, 1-year exposure to strontium ranelate significantly prevented alteration of bone mechanical properties of vertebrae in association with a partial preservation of the trabecular microarchitecture. Finally after limb immobilization SR prevented microarchitectural deterioration, while no significant alteration was observed in crystal characteristics and degree of mineralization after SR administration in monkeys.

Keywords: Strontium Ranelate, Bone Strength, Postmenopausal Osteoporosis

Osteoporosis has become an epidemic debilitating disease. It is estimated that by the end of the first postmenopausal decade half of women have osteopenia or osteoporosis¹. Furthermore, less than one-third of the cases have been diagnosed, while only one-seventh of postmenopausal women with osteoporosis receive treatment¹, thus increasing the socioeconomic burden of the disease.

Bone fragility is dependent on several inter-related parameters, such as bone mass, bone structural properties such as geometry and microarchitecture and material properties of the bone tissue². All these parameters independently influence bone fragility and are modulated by the rate of bone remodeling. Although bone mineral density (BMD) testing has served for several years as the main diagnostic modality

for the assessment of fracture risk, it soon became evident both from epidemiologic cohort studies and intervention studies with anti-catabolic agents that changes in BMD explain no more than 50% of the variability of fracture incidence.

Currently the available therapies for osteoporosis are classified either as anti-catabolic or anabolic agents³, thus targeting only one of the aspects of bone remodeling. Specifically anti-catabolic agents, such as bisphosphonates, HRT, raloxifene and calcitonin reduce activation frequency and bone resorption, thus increasing bone mass mainly by increasing mineralization and preventing micro-architectural deterioration of bone tissue. However there is solid evidence from both histomorphometry and biochemical markers of bone turnover that they also decrease bone formation. On the contrary anabolic agents, such as teriparatide and full length parathyroid hormone, reduce fracture risk by stimulating the formation of new bone both by a mechanism termed renewed modeling and by increasing bone turnover in favor of bone formation, thus increasing bone mass and improving bone architectural properties.

Strontium ranelate, which consists of 2 atoms of stable strontium and an organic acid, ranelate, is a new orally administrated drug for the treatment of postmenopausal

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osteoporosis^{4,5}. Contrary to other drugs used in osteoporosis treatment, which act by either increasing bone formation or decreasing bone resorption, strontium ranelate does both simultaneously. It increases bone cell replication and bone formation *in vitro*, by amplifying the pre-osteoblastic cells replication and by secondary or primary increases synthesis of bone matrix⁶. By monitoring the expression of carbonic anhydrase and fibronectin receptor it was concluded that the osteoclast differentiation is decreased by SR, leading to inhibition of bone resorption⁷. Strontium's suppressing activity is also established in cell cultures⁸, where a decrease of the resorption surface has been observed^{7,8}. Furthermore in the OVX rat model SR reduced bone resorption, while it maintained high bone formation⁹. In addition, a decrease of the osteoclast facies has been proven in other studies with estrogen-deficient rats.

The effect of SR on bone strength indices has been investigated in several animal models, including intact female and male rats, ovariectomized rats, after rat limb immobilization and in monkeys. In intact rats¹⁰, SR administration for two years resulted in favorable effects on both trabecular and cortical bone microarchitecture. Specifically there was a significant increase in bone volume, trabecular thickness and number, while no increase was observed in osteoid thickness indicating neutral effects on mineralization. Moreover there was a significant increase in periosteal diameter, which showed linear association with maximal load, explaining 55% of its variability. Furthermore, biomechanical testing at the vertebral body and midshaft femur showed significant increase in maximal load, especially in total and plastic energy, while stiffness was comparable compared with controls. These results indicate that SR exerts positive effects on bone strength, especially on the ability of bone to absorb energy by deformation. In the rat model of ovariectomy¹¹, which resembles postmenopausal osteoporosis, SR administration resulted in partial preservation of bone mass and microarchitectural properties. Interestingly, maximal load and ultimate strength were comparable to control rats, probably due to favorable effects on intrinsic bone biomechanical properties tested by the nano-indentation technique. In the immobilization rat model, a state characterized by increased bone resorption and reduced bone formation¹², SR administration for only 10 days significantly attenuated the decrease in BMD and the microarchitectural deterioration.

The effect of SR on mineralization and crystal characteristics has been investigated in monkeys¹³. By X-ray microanalysis, X-ray diffraction, and quantitative microradiography Farlay et al. showed that SR is dose-dependently taken up by new compact and cancellous bone, is heterogeneously distributed and rapidly eliminated after treatment withdrawal. Furthermore the mean degree of mineralization and the heterogeneity index was comparable with the control animals. Finally, crystal characteristics were preserved indicating that SR is only faintly linked to crystals by ionic substitution.

In conclusion, SR dual action on bone turnover is a breakthrough in the treatment of postmenopausal osteoporosis.

The data presented clearly establish that SR has favorable effects in almost all aspects of bone quality, which as clinical trials showed is translated into anti-fracture efficacy.

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