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Trajectories of Bone Remodeling Markers and Bone Mineral Density during Treatment with Strontium Ranelate in Postmenopausal Women Previously Treated with Bisphosphonates

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ABSTRACT

OBJECTIVE: To evaluate the responses of C-terminal telopeptide (CTX) and serum osteocalcin after the first 4 months of treatment with strontium ranelate (SR) and demonstrate their association with long-term bone density changes.

SUBJECTS AND METHODS: A sample of 13 postmenopausal women with osteoporosis was analyzed (mean age 65 ± 7.7 years), who were treated with SR for an average of 2.56 ± 0.86 years. All patients had undergone previous treatment with bisphosphonates for an average period of 4.88 ± 2.27 years. Serum CTX and osteocalcin levels were determined before and after four months of treatment with SR. Bone mineral density in the lumbar spine and femoral neck were obtained before and after treatment with SR.

RESULTS: We observed an average increase of 53.7% in the CTX levels, and 30.7% in the osteocalcin levels. The increase in bone markers was associated with a mean 4.8% increase in lumbar spine bone mineral density (BMD) from 0.820 to 0.860 g/cm^2 (T-score from –2.67 to –1.92; $P = 0.001$), after 2.5 years of treatment with SR.

CONCLUSION: These data suggest an anabolic effect of SR on postmenopausal women who were previously treated with long-term bisphosphonates.

KEYWORDS: CTX, osteocalcin, osteoporosis, strontium ranelate, bisphosphonates

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Introduction

A range of pharmacological interventions are available for the treatment of postmenopausal osteoporosis, including anti-resorptive as well as anabolic agents.[1] While mono-therapy is the most common treatment approach for the majority of patients, combined or sequential therapy with antiresorptive and anabolic agents may also be used in some cases.[1,2] This treatment modality has attracted increased interest in recent years because of the potential synergistic effect on bone strength,[3,4] as well as the fact that particularly with potent antiresorptive agents, it may be desirable to limit the duration of therapy for a finite period of time, for example five years[5] and that some other form of treatment may be required in individuals who remain at high risk for fractures after this period. Furthermore, in patients who develop intolerance to treatment, and move to another alternative, the question arises as to whether the initial treatment, especially if it was a bisphosphonate, will affect the response to subsequent pharmacological intervention.[2]

Strontium ranelate (SR) is an effective agent for the treatment of osteoporosis, reducing the incidence of vertebral and non-vertebral fractures.[6–8] Its mechanism of action has yet to be clearly established.[3] In humans, there is evidence of weak effects on bone remodeling,[9] but it is difficult to explain the

well-documented anti-fracture efficacy of the drug based on these effects, and changes in material properties of the bone may be more important.[10–14]

Although in clinical practice it is not uncommon to change treatment from bisphosphonates to SR, there is little data evaluating the response of bone mineral density because of SR treatment in patients previously treated with bisphosphonates. It is known that after discontinuation, bone turnover continues to be suppressed,[3,15,16] and that this may have consequences in the response to subsequent treatments for osteoporosis.

The aim of this study was to describe bone turnover marker responses (osteocalcin and C-terminal telopeptide (CTX)), in the first 4 months of treatment with SR, and its relationship with subsequent long-term responses of bone mineral density in postmenopausal women with osteoporosis previously treated with bisphosphonates.

Subjects and Methods

All patients were diagnosed with osteoporosis by dual energy X-ray absorptiometry (DXA) (*T*-score ≤ 2.5 SD), and had at least one radiographic vertebral fracture. The patients were treated daily with SR, 2 g at bedtime (two hours after eating), accompanied by 1.2 g of calcium (administered in the morning) and 800 IU of vitamin D per day to keep serum levels of 25(OH)D above 30 ng/mL. All patients were at least five years postmenopausal, and none had received hormone replacement therapy. We excluded patients with secondary causes of osteoporosis, patients with medical conditions associated with bone loss, as well as patients previously treated with teriparatide.

Bisphosphonates were discontinued for medical reasons (GI intolerance) or because of more than five years of use associated with reaching the extent of the plateau in measurement of bone mineral density. The mean duration of bisphosphonate therapy was 4.8 years, and SR treatment was initiated immediately after bisphosphonate treatment was terminated.

The study was approved by the local ethics committee (CEP-HAM).

Baseline values were determined for calcium, parathormone (PTH), creatinine, 25-hydroxy-vitamin D (electrochemical luminescence), alkaline phosphatase, complete blood count, albumin, and urinary calcium excretion during 24 hours. Serum levels for osteocalcin and beta-CTX were measured at the beginning, after four months, and at the end of treatment with SR. Bone mineral density (BMD) was measured by DXA at the lumbar spine (L1–4) and femoral neck, before starting and at the end of SR treatment.

Serum beta-CTX levels were measured by electrochemical luminescence (Elecsys Systems, Roche Diagnostics, Mannheim, Germany). The minimum detection limit was 10 pg/mL, and the coefficients of intra-assay and inter-assay variations were 10 and 12%, respectively. Serum osteocalcin levels were also determined by electro-chemical luminescence (Elecsys Systems, Roche Diagnostics, Mannheim, Germany), with the detection range of 0.5–300 ng/mL, with minimum detection limit of 0.5 ng/mL. The coefficients of intra-assay and inter-assay variations were 4 and 8%, respectively.

To analyze the data, distributions both in absolute terms and in percentage were obtained, along with varied single and bi values of the variables in a nominal scale derived from the following measurements: mean, standard deviation, and standard error for the numeric variables (descriptive statistic techniques). *F*-tests were used (ANOVA for repeated measurements), and in cases where significant differences existed, paired comparison tests were used for differences that were minimally significant. The significance level used in the statistical analysis was 5%. The software used to obtain the statistical calculations was SPSS (Statistical Package for Social Sciences), version 11.

Results

A total of 13 female patients with 18.31 ± 9.67 years of menopause, mean age 65.69 ± 7.70 years, and previously treated with bisphosphonates for an average of 4.8 ± 2.27 years were then submitted to treatment with SR for an average of 2.56 ± 0.86 years (Table 1).

After four months of treatment with SR, there were increases in the serum levels of osteocalcin and beta-CTX. The average levels of beta-CTX measured 174.82 ± 160.53 pg/mL before and 268.85 ± 100.48 pg/mL after four months of treatment, with a mean percentage increase of 53.7% ($P = 0.099$). There were also increases in serum osteocalcin, with a mean percentage increase of 30.7% after the fourth month of treatment ($P = 0.213$) (Figs. 1 and 2).

The increase in bone markers was associated with a mean 4.8% increase in lumbar spine BMD from 0.820 to 0.860 g/cm^2 (*T*-score from –2.67 to –1.92; $P = 0.001$), after 2.5 years of treatment with SR (Fig. 3). In the femoral neck, the mean BMD was 0.680 g/cm^2 (mean *T*-score of –2.17SD) at the beginning and 0.700 g/cm^2 (mean *T*-score of –1.88SD) at the end of treatment, corresponding to an increase in BMD of 2.94% ($P = 0.39$).

Table 1. Baseline characteristics of study population.

VARIABLES	MEAN ± SD
Age (years)	65.69 ± 7.70
Years since menopause	18.31 ± 9.67
Length of bisphosphonate use (years)	4.88 ± 2.27
Years of strontium ranelate use	2.56 ± 0.86
BMI (kg/m^2)	21.94 ± 3.05
25(OH)D (ng/mL)	31.58 ± 8.46
CTX (pg/mL)	174.82 ± 160.53
Osteocalcin (ng/mL)	12.67 ± 6.55

Abbreviations: BMI, body mass index; 25(OH)D, 25-hydroxy-vitamin D; CTX, C-terminal telopeptide.

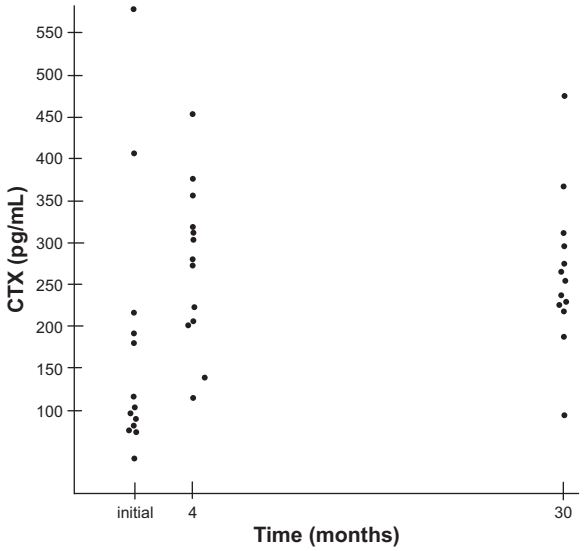

Figure 1. Changes in serum CTX during treatment with SR in post-menopausal women previously treated with bisphosphonates.
Abbreviation: CTX, C-telopeptide terminal.

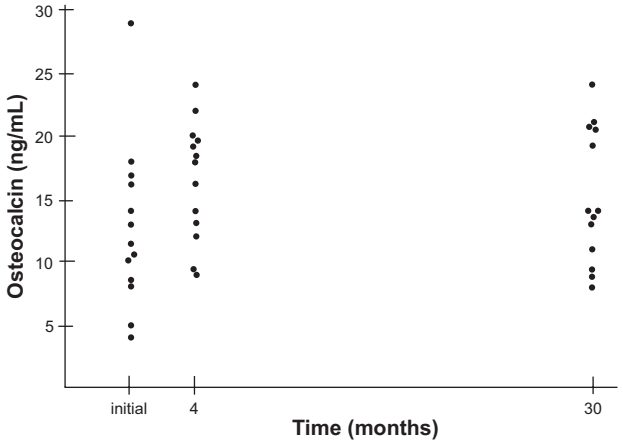

Figure 2. Changes in serum osteocalcin during treatment with SR in post-menopausal women previously treated with bisphosphonates.

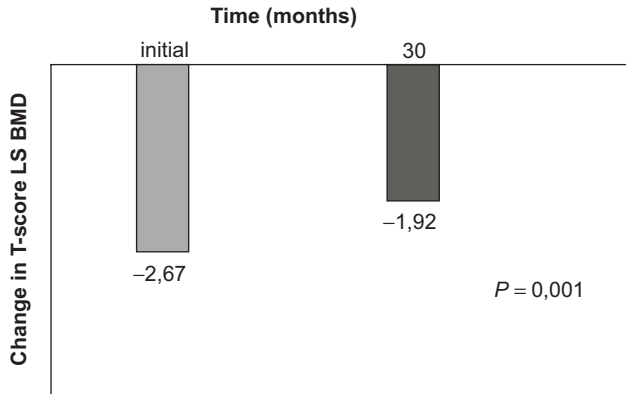

Figure 3. Changes in lumbar spine bone mineral density (*T*-score) during treatment with SR in post-menopausal women previously treated with bisphosphonates.
Abbreviations: BMD, bone mineral density; initial BMD = 0.820 g/cm^2; BMD after 30 months = 0.860 g/cm^2.

Discussion

SR has been shown to reduce the incidence of vertebral and non-vertebral fractures in postmenopausal women.[6,7,14] Once absorbed via the gastrointestinal tract, the active component strontium is embedded in the bone, resulting in increased bone formation and a reduction in bone resorption.[9] It is believed that this leads to a positive balance in terms of remodeling the basic multi-cellular units and an overall gain in bone tissue at each remodeling cycle. Studies using computerized micro-tomography (micro-CT) show that, compared to treatment with a placebo, women treated with SR have an increased number of trabecule, a better trabecular structure index, a reduction in trabecular space, and an increase in cortical thickness.[10] Compression tests confirm that treatment with SR leads to an improvement in the mechanical properties of the bone and an overall increase in bone strength.[11]

There are relatively few studies evaluating the issue of change in therapy for osteoporosis, although this is a frequent occurrence in clinical practice. Women who are taking oral bisphosphonates may be candidates for the use of SR if they develop adverse effects from the bisphosphonate treatment, such as esophagitis, or if they have an unsatisfactory response to it.[16] A recent report by Sousa et al,[17] from our institution, has shown a 25–49% increase in serum osteocalcin ($P = 0.002$) and an 80% increase in serum β-CTX ($P = 0.008$) after four months of treatment with SR, suggesting a predominantly short-term effect on bone formation in postmenopausal women previously treated with bisphosphonates.

Bisphosphonates are potent inhibitors of bone turnover, and the effects of some of them may persist long after discontinuation of therapy.[15,16] Available data so far indicate that prior administration of bisphosphonates inhibits or slows the response of subsequent administration of bisphosphonates, PTH, denosumab, and SR.[3] Continuous inhibition of bone remodeling, leading to a reduction in the formation of new bone, even after the discontinuation of bisphosphonates, provides two theoretical reasons why the prior therapy with bisphosphonates may inhibit subsequent response of bone mineral density with SR. First, because strontium is deposited predominantly in newly formed bone tissue,[12,13,18,19] previous exposure to bisphosphonates would be expected to inhibit the incorporation of strontium in hydroxyapatite crystals.[20] Second, it has been disclosed that alendronate can neutralize the anabolic properties of teriparatide,[21–23] and if SR has anabolic effects, therefore, prior exposure to bisphosphonates can also lead to similar inhibition of these bone-forming properties.

The inhibition of strontium uptake in bone leading to a lower X-ray attenuation and/or reduced bone formation would be expected to give rise to a blunting of the BMD response to SR. However, in our study we demonstrated that increases in the serum levels of osteocalcin and beta-CTX after four months of treatment with SR could be associated with higher gain in bone mass in the lumbar spine.

Findings similar to our study, but involving only patients not having used bisphosphonates, were demonstrated by Bruyère et al[24] in a recent post hoc analysis of the Spinal Osteoporosis Therapeutic Intervention (SOTI) and TReatment Of Peripheral OSteoporosis (TROPOS) trials, involving 2373 women with postmenopausal osteoporosis treated with SR. In this study, after three months of treatment with SR, bone alkaline phosphatase (BALP) increased by 9.6% (28.3) and propeptídeo carboxiterminal do procolágeno tipo 1 (PICP) by 9.9% (24.3), serum collagen type 1 cross-linked C-telopeptide (s-CTX) was reduced by 5.9% (33.3), and urinary N-telopeptide of type I collagen (u-NTX) increased by 1.1% (42.4). After three years, BMD increased by 14.4% (11.6) in the lumbar spine, 5.5% (7.8) in the femoral neck, and 7.1% (8.2) in total proximal femur. Multiple regression analysis showed that changes in bone formation markers (PICP and BALP), but neither in s-CTX nor u-NTX I, were significantly ($P < 0.001$) associated with increased BMD in the lumbar spine and femoral neck, suggesting a predominantly anabolic effect of therapy with SR.

The first study to investigate BMD response to SR after previous treatment with bisphosphonates was conducted by Middleton et al[25] who, in a prospective analysis, evaluated postmenopausal women with osteoporosis, or low BMD (*T*-score < -2) and fractures. The group was composed of 56 women who had never been treated with bisphosphonates, and 52 women who had been treated with oral bisphosphonates for at least one year and had discontinued therapy in the last month because of adverse effects or inadequate response. Both groups of women were treated daily with 2 g of SR, together with calcium and vitamin D supplements. After one year of treatment, the BMD of the lumbar spine increased by 5.6% in the group of bisphosphonate naïve patients and 2.1% in women who had previously been treated with bisphosphonates; during the 6th as well as the 12th month, the BMD increases in the femoral neck were significantly lower in the first group than in the second. No significant change in BMD measurement was found in the total femur for the group of women previously treated with bisphosphonates, compared with an increase of 3.4% for the treatment-naïve group. Regarding bone markers, serum CTX, bone-specific alkaline phosphatase, and P1NP were significantly suppressed at the baseline and showed progressive increases throughout the study, mainly in those women previously treated with bisphosphonates. In a recent report from a two-year extension of this study,[26] in the group of pre-treated women, it was found that BMD increased significantly in the lumbar spine (4%) and hip (2.5%). There was an increase in serum P1NP, BSAP, and CTX levels by 55, 46, and 65%, respectively, after two years, with a parallel increase in BMD, in the group previously treated with bisphosphonates.

In a recently published study, Busse et al[27] reported the effects of SR in 15 paired samples of bone biopsies obtained from the iliac crest in women with previous exposure to bisphosphonates, demonstrating that the bone volume and trabecular thickness did not increase during the first 6 months of treatment with SR, and that significant increases in these parameters occurred after 12 months. These data are consistent with our findings, suggesting anabolic activity from the strontium in the long term.

Our study has several limitations, such as the small number of patients with no control group as well as the fact of not evaluating anti-fracture efficacy, which do not allow to draw conclusions about the real clinical benefit of combination therapy.

In conclusion, our data show that SR has a predominantly short-term stimulating effect on bone markers, which is associated with a long-term increase in bone mineral density at the lumbar spine of women with osteoporosis having been previously treated with long-term bisphosphonates.

Author Contributions

Conceived and designed the experiments: HL. Analyzed the data: FB. Wrote the first draft of the manuscript: HL. Contributed to the writing of the manuscript: JM. Agree with manuscript results and conclusions: HL, JM, FB. Jointly developed the structure and arguments for the paper: HL, JM, FB. Made critical revisions and approved final version: FB. All authors reviewed and approved of the final manuscript.

DISCLOSURES AND ETHICS

This paper was subject to independent, expert peer review by a minimum of two blind peer reviewers. All editorial decisions were made by the independent academic editor. All authors have provided signed confirmation of their compliance with ethical and legal obligations including (but not limited to) use of any copyrighted material, compliance with ICMJE authorship and competing interests disclosure guidelines and, where applicable, compliance with legal and ethical guidelines on human and animal research participants.

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