Short-term bone marker responses to teriparatide and strontium ranelate in patients with osteoporosis previously treated with bisphosphonates

Resposta dos marcadores de curto prazo a teriparatida e ranelato de estrôncio em pacientes com osteoporose previamente tratados com bisfosfonatos

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ABSTRACT

Objective: To evaluate the responses of serum β-CTX and osteocalcin in patients who were undergoing treatment with teriparatide or strontium ranelate (SR). **Subjects and methods:** We analyzed 14 patients (12 women and 2 men; mean age of 71 years) taking teriparatide, and 13 female patients (mean age of 70 years) taking SR; all the patients having previously been on bisphosphonates. Serum β-CTX and osteocalcin levels were determined before and after the first and third months of teriparatide treatment and up to the fourth month of treatment with SR. **Results:** We observed an initial significant increase in osteocalcin levels during the first month (165%, p = 0.01) followed by a peak of β-CTX (180%, p = 0.02) after the third month of treatment with teriparatide. An increase in these markers was also observed with SR: 49% in osteocalcin (p = 0.002) and 80% in β-CTX (p = 0.008). **Conclusion:** SR had a predominantly short-term bone-forming effect in postmenopausal women with osteoporosis previously treated with bisphosphonates in a lesser degree than with teriparatide. Arq Bras Endocrinol Metab. 2010;54(2):244-9

Keywords

β-CTX; osteocalcin; teriparatide; osteoporosis; bone remodeling; strontium ranelate

RESUMO

Objetivo: Avaliar as respostas do β-CTX e osteocalcina séricos em pacientes que foram submetidas a tratamento com teriparatida ou ranelato de estrôncio (RE). **Sujeitos e métodos:** Analisaram-se 14 pacientes (12 mulheres e 2 homens; idade média 71 anos) tomando teriparatida, e 13 mulheres (idade média 70 anos) tomando RE; todos os pacientes haviam previamente tomado bisfosfonatos. Níveis séricos de β-CTX e osteocalcina foram determinados antes e após o primeiro e terceiro meses de tratamento com teriparatida e no quarto mês de tratamento com RE. **Resultados:** Observou-se um aumento inicial significativo nos níveis de osteocalcina no primeiro mês (165%, p = 0,01), seguido por um pico do β-CTX (180%, p = 0,02) após o terceiro mês de tratamento com teriparatida. Aumento nesses marcadores também foi observado com RE: 49% na osteocalcina (p = 0,002) e 80% no β-CTX (p = 0,008). **Conclusão:** RE teve um efeito predominantemente na formação óssea a curto prazo em mulheres na pós-menopausa com osteoporose tratadas previamente com bisfosfonatos em menor grau que a teriparatida. Arq Bras Endocrinol Metab. 2010;54(2):244-9

Descritores

β-CTX; osteocalcina; teriparatida; osteoporose; remodelação óssea; ranelato de estrôncio

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INTRODUCTION

Osteoporosis is characterized by the deterioration of bone mass and its structure, leading to an increase in bone fragility and a higher risk of fracture (1). Although biochemical markers are not indicated for the diagnosis of osteoporosis, there is substantial evidence showing that short-term changes in serum levels may play an important role in predicting future alterations in bone mineral density or the risk of fractures (2,3).

Teriparatide was the first anabolic drug to be approved for the treatment of osteoporosis and several studies have demonstrated the importance of teriparatide in directly stimulating bone formation. Some studies have suggested that the use of bisphosphonates may attenuate the anabolic effect of parathyroid hormone (PTH) (4-6).

The action of strontium ranelate is thought to be both anabolic, stimulating the formation of new bone, and antiresorptive. Studies have demonstrated its safety and efficacy in reducing the risk of vertebral and non-vertebral fractures associated with osteoporosis (7,8). The majority of studies with strontium have used serum bone-specific alkaline phosphatase (BSAP) and serum C-terminal telopeptides (β-CTX) as markers for bone remodeling on patients who had not previously taken bisphosphonates, indicating small short-term increases in the former and decreases in the latter during the early months of treatment (7).

There are few available data on either the changes in serum osteocalcin (OST) during anabolic therapy or on the variation in this marker in patients previously treated with bisphosphonates.

The aim of the present study was to describe the responses of serum β-CTX and osteocalcin in patients with severe osteoporosis who were undergoing treatment with teriparatide or strontium ranelate, despite previous treatment with bisphosphonates.

SUBJECTS AND METHODS

The medical records of 27 patients were analyzed. All patients had been diagnosed with osteoporosis by bone densitometry and had at least one vertebral fracture on lateral spine X-ray. There was one group of 14 patients (12 women and 2 men) taking teriparatide in daily SC doses of 20 µg, and another group of 13 patients, all women, who were taking a daily 2 g dose of strontium ranelate. All patients received calcium supplementation of 1,200 mg/day. Vitamin D was also prescribed in accordance with the individual needs in order to achieve serum 25-OH-D concentrations above 30 ng/mL. All female patients had been menopausal for more than 5 years and none had received hormone replacement therapy.

The bisphosphonates were stopped for medical reasons (gastric intolerance or more than 5 years of use associated with plateau in bone density measurements). Teriparatide and strontium ranelate was initiated immediately after bisphosphonate therapy, and the median duration of bisphosphonate use was of 6 years.
The study was approved by the local Ethics Committee (CEP-HAM).

Basal values were determined for serum calcium, PTH, creatinine, 25-hydroxyvitamin-D (25OHD), alkaline phosphatase, complete blood count, albumin and 24-h urinary calcium excretion. Serum β-CTX and osteocalcin levels were measured at baseline and between the first and fourth months of treatment with teriparatide or strontium ranelate. All patients had undergone previous treatment with bisphosphonate.

Serum β-CTX levels were measured by electrochemiluminescence (Elecsys systems, Roche diagnostics, Mannheim, Germany). The measurement interval was 10-6,000 pg/mL with a lower detection limit of 10 pg/mL and the intra-assay and inter-assay coefficients of variation were 10% and 12% respectively. Serum osteocalcin levels were also evaluated by electrochemiluminescence (Elecsys systems, Roche diagnostics, Mannheim, Germany). The measurement interval was 0.5-300 ng/mL with a lower detection limit of 0.5 ng/mL. The intra-assay and inter-assay coefficients of variation were 4% and 8% respectively.

In order to analyze the data, absolute and percentage distributions were obtained, along with the uni- and bivariate values of the variables on a nominal scale of the following measurements: mean, standard deviation and standard error for the numerical variables (techniques of descriptive statistics). F-tests were used (ANOVA for repeated measurements) and, in the case of significant differences, paired comparison tests were employed for the minimum significant differences (LSD) (techniques of inferential statistics).

The significance level used in the statistical analysis was 5%. The software used to obtain the statistical calculations was the SPSS (Statistical Package for the Social Sciences), version 11.

RESULTS

All patients taking strontium ranelate were female with 21.23 ± 8.96 years since menopause, mean age of 70.23 ± 8.3 years, body mass index 23.7 ± 2.89 kg/m² and had previously been treated with bisphosphonates, of whom seven had taken alendronate, three ibandronate and three risedronate.

The majority (85.7%) of the patients taking teriparatide were women with 24.6 ± 9.7 years since menopause. The 14 patients had previously been treated with bisphosphonates nine of whom had taken alendronate and five risedronate. The mean age was 71.2 ± 11.4 years, and the mean body mass index was 23.7 ± 4.6 kg/m² (Table 1).

Table 1. Baseline characteristics of study population

	Strontium ranelate (n = 13)	Teriparatide (n = 14)
Age (years)	70.23 ± 8.3	71.2 ± 11.4
Gender	Female: 13/Male: 0	Female: 12/Male: 02
BMI (kg/m²)	23.7 ± 2.89	23.7 ± 4.6
Years since menopause	21.23 ± 8.96	24.6 ± 9.7
Basal β-CTX (pg/mL)	132.92 ± 112.96	244.5 ± 176.5
Basal osteocalcin (ng/mL)	10.63 ± 3.39	14.2 ± 4.0
Previous bisphosphonate use	Alendronate (n = 7) Ibandronate (n = 3) Risedronate (n = 3)	Alendronate (n = 9) Risedronate (n = 5)

In patients taking teriparatide, there was an increase in mean serum β-CTX during the study period with a significant difference between the different points in time (p = 0.02), but with a greater increase of 180% from baseline to the third month. The increase from baseline for the first month was 36% and from the first to the third month 125%.

In relation to osteocalcin, the mean rise from baseline to the first month was 165% (p = 0.01), with an additional increase (11%) from the first to the third month.

In the patients who had taken strontium ranelate statistically significant increases in serum β-CTX and osteocalcin were observed. Mean serum β-CTX increased from 132.92 pg/mL to 235.24 pg/mL up to the fourth month of treatment, with a mean percentage change of 79.99% (p = 0.008). Osteocalcin also increased significantly, showing a mean percentage change of 48.73% up to the fourth month of treatment (p = 0.002) (Figures 1 and 2).

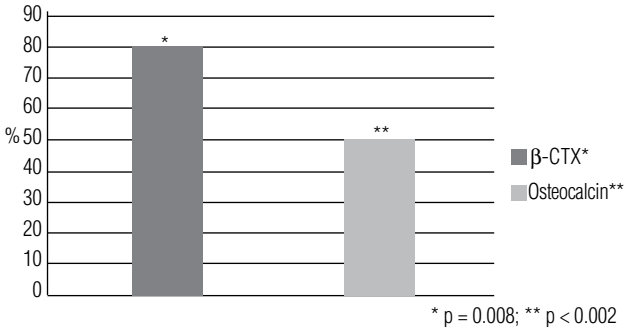

Figure 1. Percent changes in serum β-CTX and osteocalcin after 4 months of therapy with strontium ranelate in patients with osteoporosis previously treated with bisphosphonates.

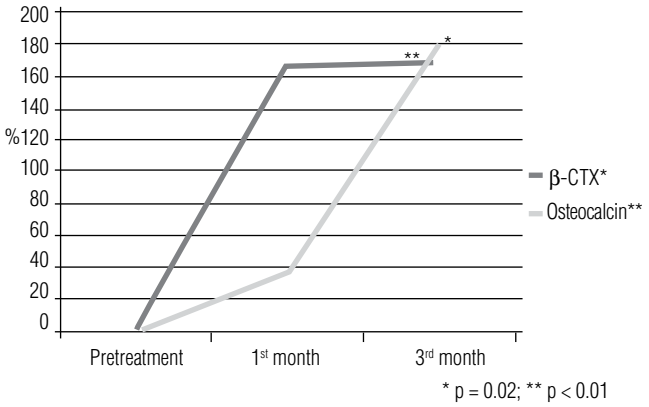

Figure 2. Percent changes in serum β-CTX and osteocalcin after 1 and 3 months of therapy with teriparatide in patients with osteoporosis previously treated with bisphosphonates.

DISCUSSION

The use of bone formation and bone resorption markers may allow a better evaluation of the action of anabolic and antiresorptive drugs used for treating osteoporosis. It has been well demonstrated how antiresorptive agents reduce the rate of bone remodeling with a decrease in bone resorption and bone formation markers (9-12). In the present study we observed the changes in bone markers in patients who were taking two classes of anabolic agents and who had previously been on bisphosphonates.

In the group of 14 patients taking teriparatide, it was observed that the increase in β-CTX was greater after 3 months of treatment, while the increase in osteocalcin was greater in the first month, thus demonstrating a greater stimulation of initial bone formation.

Studies in humans and animals suggest that the stimulation of remodeling caused by PTH does not

lead to deterioration of the mechanical properties of the bone, or to an increased risk of fractures, even in the early stages of the treatment. There are a number of reasons for this: the markers associated with bone formation increase earlier than those associated with resorption suggesting that there is an initial period during which bone formation occurs on the bone surface without resorption. This initial period protects the patient from minor late transient losses, which may occur during remodeling (13). Moreover, the increase in remodeling occurs on the trabecular surface or close to the endosteal surface of the bone where the mechanical effect is minimal. Furthermore, this transient loss may be compensated for by periosteal apposition, which maintains the overall resistance of the bone, thus preventing mechanical deterioration (14-16).

A similar finding to that of the present study but involving different bone markers was demonstrated by McClung and cols. (17). The N-propeptide of type I collagen (PINP), a bone formation marker, displayed a significantly greater increase during the first month with a peak in the sixth month of treatment when compared to N-terminal Telopeptides (NTX), a marker of bone resorption which also peaked in the sixth month but with a significantly lower increase (58% *versus* 218% of PINP) (17). On the other hand, Black and cols. (18) found a slight increase in CTX levels during the first three months of treatment with PTH in a group of postmenopausal women, followed by a modest decrease.

The importance of these short-term increases in bone markers lies in the fact that this is subsequently correlated with the increase in bone mass, as demonstrated by Dobnig and cols. (19), who evaluated 1,637 postmenopausal women taking teriparatide or placebo. They showed that the increase in serum bone specific alkaline phosphatase and PINP in the first month had a positive correlation with the histomorphometric indices by computerized microtomography (μCT) after 22 months of treatment, while changes in the markers after 6 months and 1 year were not associated with any change in the structural or dynamic parameters (19).

In a study conducted by Bauer and cols. (20) in postmenopausal women on PTH (1-84) there was an increase in serum PINP levels of 80% and 148% and in serum β-CTX levels of 5% and 64% in the first and third months, respectively. This early change in the levels of bone remodeling markers was associated with long-term increase in bone mineral density of the lumbar spine and femoral neck (20).

The concomitant use of antiresorptive drugs (alendronate) and PTH has not demonstrated any synergistic effect when compared to the isolated use of PTH (1-84). In a study by Hodsman and cols. (21), the use of PTH in postmenopausal women revealed an increase in bone mass two times greater than in PTH combined with alendronate (21). However, another study has shown that alendronate enhances the effect of teriparatide on bone turnover in men (22).

The EUROFORS study showed that the use of teriparatide was associated with a significant improvement in the structural variables, obtained by high resolution CT, and bone mineral density in patients with an inadequate response to previous antiresorptive treatment, including bisphosphonates (23).

In the group of 13 patients who had been on strontium ranelate we observed an increase in serum β-CTX, with a mean percentage change of 79.9%. An increase was also observed in serum osteocalcin, which demonstrated a mean percentage increase of 48.7%. The SOTI study, which reported a reduction in vertebral fractures in patients taking strontium ranelate, observed an 8.1% increase in serum bone specific alkaline phosphatase, and a 12.2% reduction in serum β-CTX during the first three months. These values continued to increase after this period and remained above baseline after a period of 12 months, although still at lower levels than the placebo group (7).

Our baseline levels of serum markers were lower, as expected from the previous bisphosphonate therapy, than in other studies and the lower turnover may cause more retention of strontium ranelate in bone tissue. On the other hand, stopping bisphosphonate therapy would lead to recovery of bone turnover, although this would have occurred in a more gradual manner and would not have been observed in a period as short as four months and with such a significant increase (24). Our results are in agreement with a recent post-hoc analysis of 2,373 women from the SOTI and TROPOS data in which 3-month changes (mean 10% increase; highest quartile > 21% increase) in C-terminal propeptite of type I collagen (P1CP) and serum BSAP were significantly associated with 3-year bone mineral density increases in the lumbar spine and femoral neck, suggesting a predominant anabolic effect of strontium ranelate therapy (25).

Four of our patients whose markers were evaluated after a 12-month period of treatment still presented higher levels than the basal and fourth month levels, along with an increase in BMD.

One other study that evaluated the short-term changes in bone turnover markers in patients who had taken strontium ranelate or teriparatide indicated significant 3-month increases in serum P1NP (14%) with teriparatide and a slight decrease in P1NP and serum β-CTX (11%) with strontium ranelate in 22 patients with no previous use of bisphosphonates (26). No significant differences were demonstrated in histomorphometric parameters from transiliac bone biopsies between both teriparatide and strontium ranelate groups after six months of therapy. Mineral apposition rate and bone formation rate correlated significantly with the 3-month changes in P1NP in the teriparatide treated group.

The reasons for conflicting data regarding short-term responses to bone-formation markers after starting strontium ranelate in women without previous use of bisphosphonates are unclear, but it seems that strontium ranelate may induce different responses to different markers. Osteocalcin is produced directly by osteoblasts and as strontium ranelate induces osteoblasts replication, the response to osteocalcin may well be more rapid and pronounced as it was seen in our study. In the earlier controlled trials in women without previous use of bisphosphonates there were no differences in the magnitude of serum osteocalcin (measured by IRMA) elevations between strontium ranelate and placebo, but these results may have been influenced by the fact that lower doses (185 mg, 500 mg, 1 g) were used (27,28). Finally, the possibility of combination or sequential therapy with strontium ranelate should not reduce the beneficial effects of bisphosphonates on bone turnover and the combined effects of the two drugs on bone strength might be synergistic (29).

In conclusion, our data show that strontium ranelate has a predominantly short-term stimulating effect on bone formation and resorption markers in postmenopausal women with osteoporosis previously treated with bisphosphonates although to a lesser degree than teriparatide.

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