

ORIGINAL ARTICLE

The Effects of Strontium Ranelate on the Risk of Vertebral Fracture in Women with Postmenopausal Osteoporosis

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ABSTRACT

BACKGROUND

Osteoporotic structural damage and bone fragility result from reduced bone formation and increased bone resorption. In a phase 2 clinical trial, strontium ranelate, an orally active drug that dissociates bone remodeling by increasing bone formation and decreasing bone resorption, has been shown to reduce the risk of vertebral fractures and to increase bone mineral density.

METHODS

To evaluate the efficacy of strontium ranelate in preventing vertebral fractures in a phase 3 trial, we randomly assigned 1649 postmenopausal women with osteoporosis (low bone mineral density) and at least one vertebral fracture to receive 2 g of oral strontium ranelate per day or placebo for three years. We gave calcium and vitamin D supplements to both groups before and during the study. Vertebral radiographs were obtained annually, and measurements of bone mineral density were performed every six months.

RESULTS

New vertebral fractures occurred in fewer patients in the strontium ranelate group than in the placebo group, with a risk reduction of 49 percent in the first year of treatment and 41 percent during the three-year study period (relative risk, 0.59; 95 percent confidence interval, 0.48 to 0.73). Strontium ranelate increased bone mineral density at month 36 by 14.4 percent at the lumbar spine and 8.3 percent at the femoral neck ($P < 0.001$ for both comparisons). There were no significant differences between the groups in the incidence of serious adverse events.

CONCLUSIONS

Treatment of postmenopausal osteoporosis with strontium ranelate leads to early and sustained reductions in the risk of vertebral fractures.

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VERTEBRAL FRACTURES, A SERIOUS CONSEQUENCE of osteoporosis, lead to acute and chronic back pain, spinal deformity, and a reduction in survival equivalent to that caused by hip fractures.¹ The health care burden in financial terms is substantial.² Vertebral deformities predict further vertebral fracture, even within one year, and also predict nonvertebral fractures.^{1,3,4}

The bone fragility that characterizes osteoporosis after menopause results both from an imbalance in bone remodeling at the cellular level, which causes bone resorption to exceed bone formation, and from an increase in the rate of remodeling at the tissue level.⁵ Antiresorptive therapies reduce the rate of bone remodeling and lower the fracture rate by 30 to 50 percent. Antiresorptive agents, however, do not increase bone tissue mass. Instead, the increase in bone mineral density observed in clinical trials of antiresorptive drugs is the result of a more complete secondary mineralization of the existing (but reduced) bone tissue mass.⁶⁻¹⁰ Restoration of bone tissue mass and bone structure is not achieved with antiresorptive drugs and requires the use of anabolic agents.^{11,12}

Strontium ranelate is a new orally active agent consisting of two atoms of stable strontium and an organic moiety (ranelic acid). It stimulates the formation of new bone tissue and decreases bone resorption, as has been shown in vitro and in experiments in animals.¹³⁻¹⁶ Strontium ranelate prevents bone loss in ovariectomized rats, increases bone mass in osteopenic animals, and increases bone strength in normal animals.^{13,17,18} To date, no deleterious effects on the primary or secondary mineralization of bone in laboratory animals^{18,19} or humans²⁰ have been reported. Results from a two-year placebo-controlled, phase 2, dose-response study involving 353 postmenopausal women with osteoporosis suggested that ingestion of 2 g a day of oral strontium ranelate reduced the incidence of vertebral fractures during the second year of treatment and simultaneously increased bone mineral density.²⁰ In order to confirm these results, we designed the Spinal Osteoporosis Therapeutic Intervention study to test the safety of strontium ranelate and its efficacy against vertebral fracture when given orally at a dose of 2 g per day for three years in postmenopausal women with osteoporosis and a history of vertebral fracture.

METHODS

STUDY SUBJECTS

We recruited postmenopausal women from November 1996 through July 1998 at 72 centers in 11 European countries and Australia for this prospective, randomized, double-blind, placebo-controlled trial. Women were eligible for the study if they were at least 50 years old, had been postmenopausal for at least five years, had had at least one fracture confirmed by spinal radiography (after minimal trauma), and had a lumbar-spine bone mineral density of 0.840 g per square centimeter or less (measured with Hologic instruments). Women were ineligible if they had severe diseases or conditions that could interfere with bone metabolism or if they used anti-osteoporotic treatments (fluoride salts and bisphosphonates taken for more than 14 days within the previous 12 months, or estrogen, calcitonin, or calcitriol taken for more than 1 month in the previous 6 months). All participants provided written informed consent before enrollment in the study; the study was approved by the institutional review board at each center.

TREATMENT PROTOCOL AND FOLLOW-UP

Throughout the study, subjects received daily calcium supplements at lunchtime (up to 1000 mg of elemental calcium, depending on their dietary calcium intake), to maintain a daily calcium intake above 1500 mg, and vitamin D (400 to 800 IU, depending on the base-line serum concentration of 25-hydroxyvitamin D). After a run-in period of 2 to 24 weeks, depending on the severity of the deficiency of calcium and vitamin D, the subjects were randomly assigned to receive 2 g a day of strontium ranelate (two packets a day of a powder that they mixed with water) or placebo powder for 3 years. Subjects were instructed to take the study drug once daily, at bedtime, or twice daily (one packet 30 minutes before breakfast, and one at bedtime). Most subjects (87 percent) chose the once-daily regimen.

Three lateral radiographs of the spine (thoracic and lumbar radiographs and an image of the thoracolumbar junction) were obtained at base line and annually, according to standardized procedures, and if there were indications of symptomatic vertebral fracture (acute back pain, a decrease in body height of at least 1 cm, or both). At base line, anteroposte-

rior radiographs of the spine were also obtained. All radiographs were assessed at a central facility; radiologists were told the time sequence of each radiograph but were unaware of the treatment assignment.

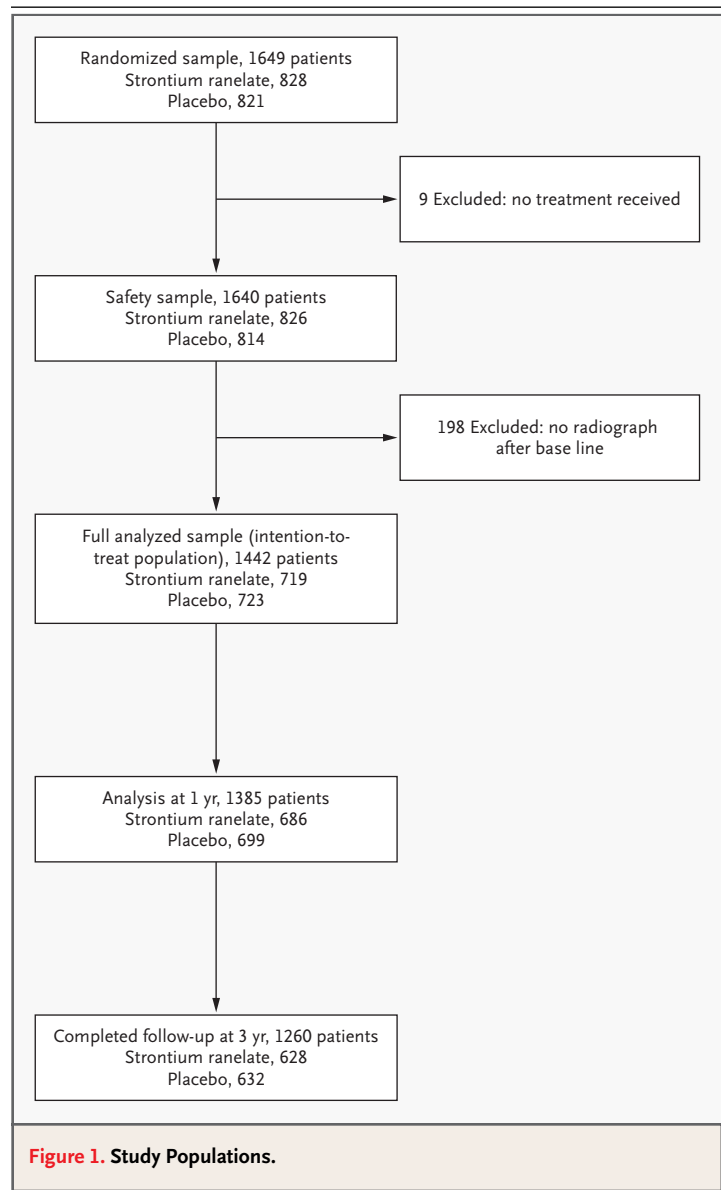
Two methods of assessing vertebral fracture were used. First, a semiquantitative visual assessment of each vertebra, from T4 to L4, was performed by the same reader throughout the study. The semiquantitative grading scale was as follows: grade 0, normal; grade 1, a decrease in the height of any vertebra of 20 to 25 percent; grade 2, a decrease of 25 to 40 percent; and grade 3, a decrease of 40 percent or more.^{21,22} For primary analysis, a new fracture was defined by a change in the score of a vertebra from grade 0 at base line to a subsequent grade of 1 or more. Second, quantitative assessment was also performed: anterior, middle, and posterior vertebral heights were measured for each vertebra, from T4 to L4. A new fracture was defined by a decrease in height of at least 15 percent (or 3 mm) on a vertebra graded 0 at base line and with a grade on the semiquantitative scale of 1, 2, or 3.²³

Nonvertebral fractures were confirmed by a radiologic evaluation or by a report from a hospitalization. (The study did not have sufficient power for adequate statistical comparison of the two groups.) Skull, face, finger, toe, and coccygeal fractures were not considered to be osteoporotic fractures. Standing height was measured at base line and every six months with a Harpenden stadiometer, according to a standardized procedure.

Bone mineral density at the lumbar spine and proximal femur was measured by dual-energy x-ray absorptiometry at base line and at six-month intervals (Hologic). All the scans were analyzed centrally. A quality-control program was conducted throughout the study.²⁴ Lumbar-spine bone mineral density, adjusted for the strontium content of the bone, was calculated at month 36 according to the following formula²⁰: $\text{adjustment factor} = 1 \div [1 + (\text{estimated bone strontium content} \times 0.61)]$, with bone strontium content defined as the value measured in bone-biopsy samples obtained in some subjects at month 36.

Blood and urine samples were collected at base line, three months, and six months, and then every six months; the samples were stored at -80°C and analyzed centrally. Biochemical tests were performed by Bio Analytical Research Corporation (BARC) according to standard methods. Serum con-

centrations of bone-specific alkaline phosphatase (a marker of bone formation) were measured with an immunoradiometric assay (Tandem-R Ostase, Hybritech), serum concentrations of C-telopeptide cross-links (a marker of bone resorption) with an enzyme-linked immunosorbent assay (Serum CrossLaps, Osteometer Biotech), parathyroid hormone with an immunoradiometric assay (N-tact, DiaSorin), 25-hydroxyvitamin D with a radioimmunoassay (DiaSorin), and calcitonin with an immunoradiometric assay (Biosource). Also measured was 1,25-dihydroxyvitamin D, by means of a radi-



oreceptor assay (DiaSorin). The strontium content of serum and bone was measured with inductively coupled plasma-emission spectrophotometry (BARC), and the results were released only after the randomization code had been broken.

Biopsies of transiliac bone were carried out after tetracycline double labeling in 20 consenting patients to assess bone strontium content and safety-related histomorphometric variables.

STATISTICAL ANALYSIS

The main efficacy analysis was performed on an intention-to-treat basis and included patients who underwent randomization, who had taken at least one packet of treatment, and for whom at least one spinal radiograph was obtained after base line. Kaplan–Meier product-limit estimates of the incidence of new vertebral fractures were calculated at the time each year when radiography was performed. An unadjusted Cox model served as the main statistical analysis for the comparison of groups and the estimation of relative risks and 95 percent confidence intervals.

Two-sided Student's t-tests were used to com-

pare percent changes from base line in independent samples, the Pearson chi-square test was used to compare the numbers of patients with at least two new vertebral fractures and the numbers of patients with a specific adverse event, and 95 percent confidence intervals were determined for the differences between the groups with respect to mean changes in serum calcium, phosphorus, and parathyroid hormone levels. For percent changes from the base-line value in bone mineral density at each subsequent visit, a step-down hierarchical procedure was performed on the basis of the increasing treatment effect over time. The mean values in the two groups at each visit were compared with the use of one-sided Student's t-tests with a type I error rate of 2.5 percent. The P values presented correspond to a two-sided test at the 5 percent threshold. (One-sided P values were doubled.)

The data and assessments collected in this study were held by Servier, and statistical analyses were performed by Servier. Data concerning bone mineral density, biochemical markers and other biochemical variables, and the evaluation of spinal radiographs were collected centrally by independent investigators and then transferred to Servier for statistical analysis. The authors had access to all the data and take responsibility for the veracity of the analyses.

This study was coordinated and organized under the control of an independent advisory committee, whose members were not directly involved in the study, and the international coordinator (Dr. Meunier), who monitored the scientific quality of the studies, patient compliance and adherence to the protocol, results, and conclusions. A steering committee planned the study, its conduct, and the statistical analysis, and it oversaw any scientific or technical issues. The members of an adverse-events committee were independent of the sponsor and of other committees.

RESULTS

STUDY SUBJECTS

Of 1649 women who underwent randomization, 87.4 percent (1442 women) made up the population for the intention-to-treat analysis (Fig. 1). The base-line characteristics of the two groups were similar both in the intention-to-treat population (Table 1) and among all patients randomly assigned to treatment groups (data not shown). In the intention-to-treat population, 87.4 percent of the place-

Table 1. Base-Line Characteristics of the 1442 Patients in the Intention-to-Treat Population.*

Characteristic	Placebo (N=723)	Strontium Ranelate (N=719)
Age (yr)	69.2±7.3	69.4±7.2
Yr since menopause	21.6±8.7	22.1±8.8
Body-mass index†	26.2±4.1	26.1±4.1
Cigarette smoking (%)	11.3	12.4
Previous nonvertebral fracture (%)	32.0	33.7
No. of previous vertebral fractures	2.20±2.18	2.16±2.01
Bone mineral density at the lumbar spine		
Mean (g/cm ²)	0.720±0.118	0.731±0.125
T score	-3.6±1.2	-3.5±1.3
Bone mineral density at the femoral neck		
Mean (g/cm ²)	0.591±0.093	0.591±0.086
T score	-2.8±0.8	-2.8±0.8
Bone mineral density of the total hip		
Mean (g/cm ²)	0.681±0.113	0.685±0.109
T score	-2.4±1.1	-2.4±1.1
Serum bone-specific alkaline phosphatase (ng/ml)	12.8±4.9	12.3±4.5
Serum C-telopeptide cross-links (pmol/liter)	4181±2034	4092±2401

* Plus-minus values are means ±SD. There were no significant differences between the groups.

† The body-mass index is the weight in kilograms divided by the square of the height in meters.

bo group and 87.3 percent of the strontium ranelate group completed three years of follow-up.

VERTEBRAL FRACTURES, BODY HEIGHT, AND NONVERTEBRAL FRACTURES

At the end of the first year of treatment, there was a 49 percent lower risk of a new vertebral fracture in the strontium ranelate group than in the placebo group (incidence, 6.4 percent vs. 12.2 percent; relative risk, 0.51; 95 percent confidence interval, 0.36 to 0.74; $P < 0.001$), and a 52 percent lower risk of symptomatic fracture (3.1 percent vs. 6.4 percent; relative risk, 0.48; 95 percent confidence interval, 0.29 to 0.80; $P = 0.003$). Over the entire three-year study period, the strontium ranelate group had a 41 percent lower risk of a new vertebral fracture than the placebo group (20.9 percent vs. 32.8 percent; relative risk, 0.59; 95 percent confidence interval, 0.48 to 0.73; $P < 0.001$) (Fig. 2). On the basis of these data, 9 patients would need to be treated for three years with strontium ranelate in order to prevent 1 patient from having a vertebral fracture (95 percent confidence interval, 6 to 14).

Quantitative assessment confirmed by the semi-quantitative evaluation of vertebral fractures showed that 17.7 percent of patients receiving strontium ranelate for three years and 28.4 percent of patients receiving placebo had one new vertebral fracture that met the study criteria (relative risk in the strontium ranelate group, 0.58; 95 percent confidence interval, 0.46 to 0.73; $P < 0.001$). The proportion of patients with more than one new vertebral fracture over the three-year period was 6.4 percent in the strontium ranelate group and 9.8 percent in the placebo group (relative risk, 0.64; 95 percent confidence interval, 0.44 to 0.93; $P = 0.02$). Symptomatic vertebral fractures were detected in 192 patients (11.3 percent of the strontium ranelate group and 17.4 percent of the placebo group), corresponding to a 38 percent lower risk over a period of three years in the strontium ranelate group than in the control group (relative risk, 0.62; 95 percent confidence interval, 0.47 to 0.83; $P < 0.001$).

Over the three-year treatment period, fewer patients had height loss of at least 1 cm in the strontium ranelate group (30.1 percent) than in the placebo group (37.5 percent, $P = 0.003$). Back pain was reported by 17.7 percent of the women in the strontium ranelate group and by 21.3 percent in the placebo group ($P = 0.07$). Nonvertebral fractures occurred in 234 women (112 in the strontium ranelate group and 122 in the placebo group) over the study

period (relative risk, 0.90; 95 percent confidence interval, 0.69 to 1.17).

BONE MINERAL DENSITY, SERUM STRONTIUM LEVELS, AND MARKERS OF BONE TURNOVER

Bone mineral density was similar at base line in the two groups and increased continuously at the spine, femoral neck, and total hip in the strontium ranelate group over the three-year period, with no trend toward a plateau (Fig. 3). Over a period of three years, bone mineral density in the strontium ranelate group had increased from base line by 12.7 percent at the lumbar spine, 7.2 percent at the femoral neck, and 8.6 percent at the total hip ($P < 0.001$ for all three comparisons with base-line values), corresponding to differences between the placebo and the treatment groups at three years of 14.4 percent, 8.3 percent, and 9.8 percent, respectively. At three years, the bone mineral density at the lumbar spine, adjusted for the strontium content, showed an increase over the base-line value of 6.8 percent in the

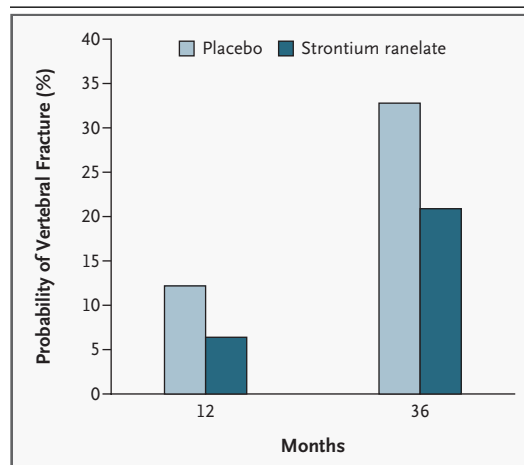
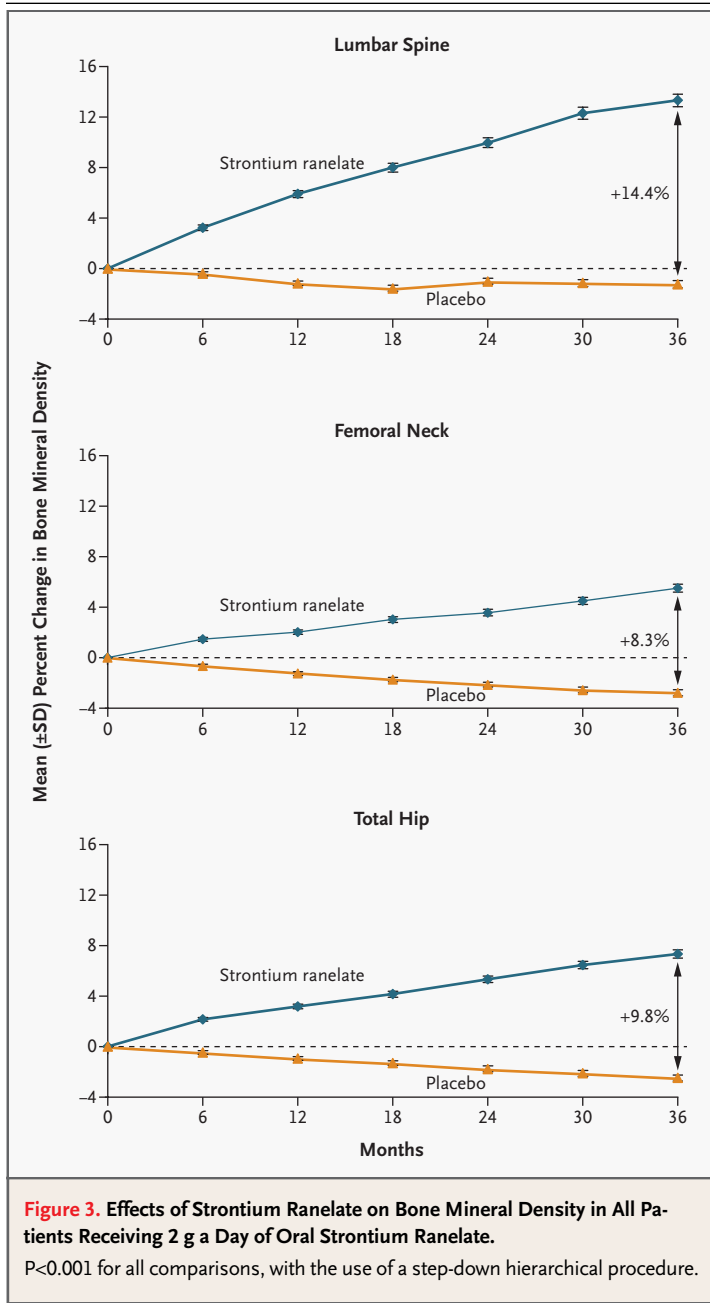


Figure 2. Proportion of Patients in the Intention-to-Treat Population Who Had One or More New Vertebral Fractures, Assessed According to the Semiquantitative Method.

Analysis at month 12 was restricted to patients with assessable radiographs at base line and at month 12 (686 patients in the strontium ranelate group and 699 in the placebo group). The relative risk of fracture in the treatment group at 12 months was 0.51 (95 percent confidence interval, 0.36 to 0.75; $P < 0.001$). Analysis for the three-year period was restricted to patients with assessable radiographs at base line and after base line (719 patients in the strontium ranelate group and 723 in the placebo group). The relative risk of fracture over 36 months was 0.59 (95 percent confidence interval, 0.48 to 0.73; $P < 0.001$).



strontium ranelate group and a decrease of 1.3 percent in the placebo group (P<0.001); these changes correspond to a treatment-related increase of 8.1 percent.

At base line, the median serum strontium concentration was 0.3 μmol per liter in both groups. At three months, the median serum strontium concentration in the treated group had risen to 117.9

μmol per liter and then reached a plateau. At the third month of therapy, the serum concentration of bone-specific alkaline phosphatase was higher in the strontium ranelate group than in the placebo group (a treatment-related increase of 8.1 percent, P<0.001), and this difference persisted at each evaluation during the three years (Fig. 4A and 4C). The concentration of serum C-telopeptide cross-links was lower in the strontium ranelate group than in the placebo group at month 3 (a treatment-related difference of 12.2 percent, P<0.001) and at each subsequent evaluation during the three years (P<0.001) (Fig. 4B and 4C).

HISTOMORPHOMETRIC FEATURES OF BONE

Bone biopsies were performed at 24, 36, or 48 months in 20 consenting patients, resulting in 14 samples that could be assessed. All biopsy specimens consisted of lamellar bone. None of the biopsies showed evidence of osteomalacia or any sign of a primary mineralization defect. As compared with the placebo group, the strontium ranelate group had no increase in osteoid thickness (P=0.64) or in the mineralization lag time (P=0.76) and no decrease in the mineral apposition rate (P=0.93).

ADVERSE EVENTS AND METABOLIC RESULTS

During the three years of the study, the rate of compliance with therapy was 83 percent in the strontium ranelate group and 85 percent in the placebo group. The rates of adverse events, serious adverse events, and withdrawal due to adverse events were similar in the two groups. Diarrhea was the most frequent gastrointestinal adverse event (occurring in 6.1 percent of the strontium ranelate group and 3.6 percent of the placebo group, P=0.02). However, this effect disappeared after the first three months. There was a lower incidence of gastritis, as diagnosed clinically by the investigators, in the strontium ranelate group than in the placebo group (3.6 percent vs. 5.5 percent, P=0.07). Serum calcium concentrations were lower and serum phosphate concentrations higher in the strontium ranelate group than in the control group at month 3, with a plateau thereafter (95 percent confidence interval for the difference between the groups, -0.32 to -0.20 mg per deciliter [-0.08 to -0.05 mmol per liter] for calcium and 0.25 to 0.37 mg per deciliter [0.08 to 0.12 mmol per liter] for phosphorus). There was a slight reduction in serum parathyroid hormone from the level at month 6 in both groups (decrease

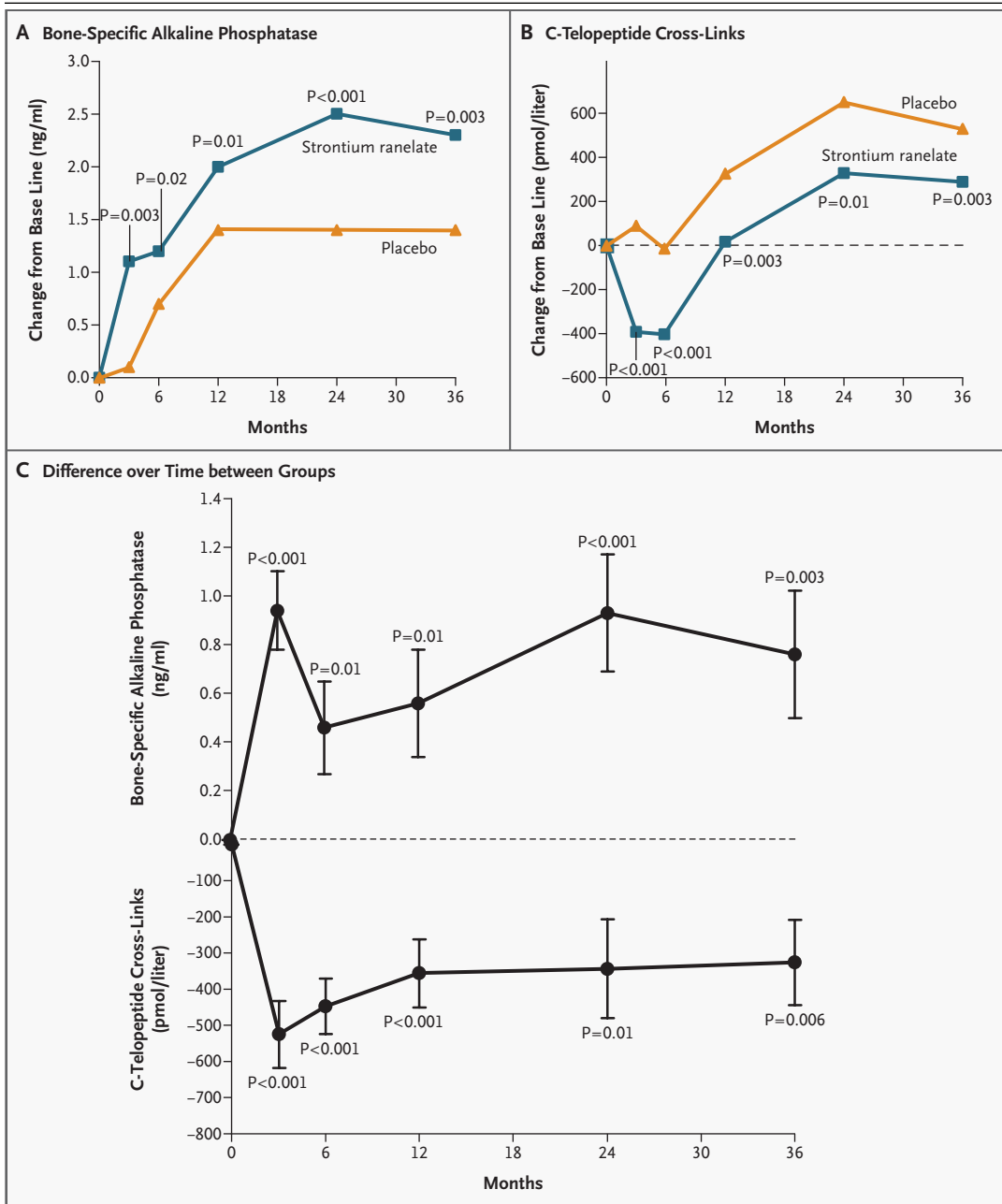


Figure 4. Strontium Ranelate–Induced Changes in Serum Biochemical Markers of Bone Metabolism.

Panel A shows absolute changes from base-line values in bone-specific alkaline phosphatase, Panel B shows absolute changes from base-line values in C-telopeptide cross-links, and Panel C shows differences over time in biochemical markers between the two groups. Data shown are mean (\pm SE) values in the strontium ranelate group minus mean values in the placebo group. Comparisons were performed with analyses of covariance in which base-line values were used as covariates.

from base-line to six-month values, -3.4 ± 10.7 pg per milliliter in the strontium ranelate group and -1.3 ± 15.8 pg per milliliter in the placebo group). No changes were observed for serum 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D, or calcitonin.

Serum creatine kinase concentrations in the skeletal muscle increased in some patients; with a high concentration defined as a value that was at least twice the upper limit of the normal range (145 IU per liter), high levels were detected in 3.4 percent of patients in the strontium ranelate group at least once during the study and in 1.8 percent of patients in the placebo group. No increase in muscular symptoms or other biologic abnormalities were observed. Most of the increases in creatine phosphokinase were transient, and in more than 88 percent of the patients who had high concentrations, the values returned to the normal range during treatment.

DISCUSSION

Prevention of fractures is the primary aim of anti-osteoporotic treatment. In the present study, strontium ranelate ingested daily reduced the risk of new vertebral fractures by 49 percent at one year and by 41 percent over a three-year period among postmenopausal women with osteoporosis. Although data from direct comparisons with other antiosteoporotic treatments are lacking, the reduction in the risk of vertebral fracture seems similar to the reduction reported with alendronate (47 percent),⁶ 5 mg of risedronate (49 percent),⁷ 60 mg of raloxifene (30 percent),⁸ and parathyroid hormone (65 percent after 21 months of treatment).¹² The methods of assessing vertebral fractures, involving both semiquantitative and morphometric evaluations, were similar to the methods used in these other reports.^{6-8,12} Strontium ranelate also reduced the risk of multiple vertebral fractures and the risk of symptomatic fractures. In this group of women, who had established osteoporosis and a history of fractures, the number needed to treat to prevent one fracture was nine.

Most antiresorptive agents prevent bone destruction by reducing the rate of bone remodeling, as reflected by a decrease in both markers of bone resorption (more than 50 percent with bisphosphonates and about 30 percent with raloxifene) and markers of bone formation (about 50 percent with bisphosphonates and 20 percent with raloxifene).²⁵ Treatment with parathyroid hormone increases both

bone formation and bone resorption.²⁶ When parathyroid hormone and alendronate are combined, there is, unexpectedly, no potentiation of their effects on biochemical bone markers.²⁷ The mechanism of action of strontium ranelate is probably different from those of these drugs. Each time the patients were evaluated during our study, bone formation had increased in the group assigned to strontium ranelate, on the basis of serum concentrations of bone-specific alkaline phosphatase, and bone resorption had decreased, on the basis of serum concentrations of C-telopeptide cross-links, as compared with the values in the placebo group. The changes in biochemical markers of bone resorption and formation were most pronounced during the first six months; the dissociation between the bone markers was evident throughout the study. The mechanisms for the apparent dissociation between reduced bone resorption and increased bone formation are not yet understood, but they probably differ from the mechanisms of current treatments.⁶⁻⁹

Any metal with an atomic number higher than that of calcium can be expected to influence bone mineral density.²⁸ In experiments, strontium in bone correlated with strontium in plasma.²⁹ In this study, strontium ranelate increased bone mineral density at three years by 14.4 percent at the lumbar spine, by 8.3 percent at the femoral neck, and by 9.8 percent at the total hip, and bone strength is directly proportional to bone mineral density. Although data from directly comparable trials are not available, the treatment effect after adjustment for the strontium content of bone was an 8.1 percent increase in bone mineral density at the lumbar spine at 3 years, which compares favorably with a 9 percent increase with parathyroid hormone (20 μ g) at 21 months and with the increases with other drugs (5.9 percent with risedronate, 6.2 percent with alendronate, and 2.6 percent with raloxifene). Moreover, this increase is consistent with the results of previous phase 2 studies involving strontium ranelate.^{20,30} In summary, strontium ranelate given orally at a dose of 2 g daily appears to reduce the risk of vertebral fractures rapidly, effectively, and safely among postmenopausal women with osteoporosis.

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APPENDIX

The Spinal Osteoporosis Therapeutic Intervention study investigators were as follows: Australia: J. Graham, Ashford Specialist Centre, Ashford; K.W. Ng, St. Vincent's Hospital, Fitzroy; R. Prince, Sir Charles Gairdner Hospital, Nedlands; J. Prins, Princess Alexandra Hospital, Woolloongabba; E. Seeman, Austin and Repatriation Medical Centre, Heidelberg; J. Wark, Royal Melbourne Hospital, Parkville; Belgium: J.Y. Reginster, Brull Hospital, Liege; J.P. Devogelaer, Catholic University of Louvain, Brussels; J.M. Kaufman, University of Gent, Gent; F. Raeman, Jan Palfijn Ziekenhuis, Merksem; M. Walravens, Medical Centre, Tessenderloo; Denmark: S. Pors-Nielsen, Hillerød Hospital, Hillerød; H. Beck-Nielsen, University Hospital Osteoporosis Centre, Odense; P. Charles, Aarhus Amtssygehus, Aarhus; O.H. Sorensen, Osteoporosis Research Center, Hvidovre; France: P.J. Meunier, Edouard Herriot Hospital, Lyons; J.P. Aquino, Medical Clinic La Porte Verte, Versailles; C. Benhamou, La Madeleine Hospital, Orleans; F. Blotman, Lapeyronie Hospital, Montpellier; O. Bonidan, E. Muller Hospital, Mulhouse; P. Bourgeois, Pitié-Salpêtrière Hospital, Paris; M.C. De Vernejoul Lariboisière Hospital, Paris; J. Dehais, Pellegrin-Tondu Hospital, Bordeaux; P. Fardellone, Nord Hospital, Amiens; A. Kahan, Cochin Hospital, Paris; J.L. Kuntz, Haute-pierre Hospital, Strasbourg; C. Marcelli, Regional Hospital and University Centre, Caen; A. Prost, Hôtel Dieu Hospital, Nantes; B. Vellas, La Grave-Casselardit Hospital, Toulouse; G. Weryha, Brabois Hospital, Vandoeuvre; Germany: E.M. Lemmel, Max Grundig Clinic, Buhl; D. Felsenberg, Benjamin Franklin Clinical University, Berlin; J. Hensen, Medical Clinic 1, Erlangen; H.P. Kruse, Medical Clinical University, Hamburg; W. Schmidt, St. Josef Hospital, Bochum; J. Semler, Immanuel Hospital, Berlin; G. Stucki, Clinic for Physical Medicine and Rehabilitation, Munich; Greece: C. Phenekos, Red Cross Hospital, Athens; Hungary: A. Balogh, University of Debrecen, Medical and Health Sciences Centre, Debrecen; R. De Chatel, Semmelweis Orvostudományi Egyetem, Budapest; Italy: S. Ortolani, Centre Auxologico Italiano, Milan; S. Adami, Hospital and Clinical Centre of Medicine, Valeggio sul Mincio; G. Bianchi, Hospital La Colletta, Arenzano; M.L. Brandi, General Hospital Careggi, Florence; D. Cucinotta, S. Orsola Malpighi Hospital, Bologna; C. Fiore, Medical Clinic, Vittorio Emanuele Hospital, Catania; C. Gennari, Institute of Medicine Clinic, New General Hospital Le Scotte, Siena; G. Isaia, University of General Medicine, Turin; G. Luisetto, University Institute of Semeiotica Medica, Padua; R. Passariello, Institute of Radiology, La Sapienza University, Rome; M. Passeri, Parma University, Parma; G. Rovetta, E. Bruzzone Institute, Genoa; L. Tessari, San Raffaele Hospital, Milan; Poland: J.E. Badurski, Center for Osteoporosis and Osteo-Articular Diseases, Białystok; K. Hozzowski, Medical Centre, Warsaw; R.S. Lorenc, Osteoporosis Centre of Krajowe, Warsaw; A. Sawicki, Warsawian Center of Osteoporosis and Calcium Metabolism Osteomed, Warsaw; Spain: A. Díez, El Mar Hospital, Barcelona; J.B. Cannata, General Hospital of Asturias, Oviedo; M. Díaz Curiel and A. Rapado, Jiménez Díaz Foundation, Madrid; J. Gijón and A. Torrijos, La Paz Hospital/Hospital de Rehabilitación y Traumatología, Madrid; J.M. Padrino, Hospital 12 de Octubre, Madrid; A. Rocas Varela, Hospital Nuestra Señora de la Candelaria, Santa Cruz de Tenerife, Canary Islands; Switzerland: J.P. Bonjour and R. Rizzoli, Geneva University Hospital, Geneva; United Kingdom: T. D. Spector, Department of Rheumatology, St. Thomas' Hospital, London; M. Clements, North London Clinical Studies Centre, Mount Vernon Hospital, Northwood; D.V. Doyle, Silverthorn Centre, Chingford; P. Ryan, Medway Hospital Trust, Gillingham; I.G. Smith, Synexus Ltd. Clinical Research Centre, Manchester; R. Smith, Banbury Clinical Studies Centre, Banbury.

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