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The Peroxisome Proliferator-Activated Receptor-γ Agonist Rosiglitazone Decreases Bone Formation and Bone Mineral Density in Healthy Postmenopausal Women: A Randomized, Controlled Trial

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Context: Thiazolidinediones, which are peroxisome proliferator-activated receptor-γ agonists, are widely prescribed to patients with disorders characterized by insulin resistance. Preclinical studies suggest that peroxisome proliferator-activated receptor-γ signaling negatively regulates bone formation and bone density. Human data on the skeletal effects of thiazolidinediones are currently available only from observational studies.

Objective: The objective of the study was to determine whether rosiglitazone, a thiazolidinedione, inhibits bone formation.

Design: The study was a 14-wk randomized, double-blind, placebo-controlled trial.

Setting: The study was conducted in the general community.

Patients: Fifty healthy, postmenopausal women participated in the study.

Intervention: Intervention was rosiglitazone 8 mg/d.

Main Outcome Measures: The primary end point was biochemical markers of bone formation, and secondary end points were a bone resorption marker and bone mineral density.

Results: The osteoblast markers procollagen type I N-terminal propeptide and osteocalcin declined by 13% ($P < 0.005$ *vs.* placebo) and 10% ($P = 0.04$ *vs.* placebo), respectively, in the rosiglitazone group. These changes were evident by 4 wk and persisted for the duration of the study. There was no change in the serum β-C-terminal telopeptide of type I collagen, a marker of bone resorption ($P = 0.9$ *vs.* placebo). Total hip bone density fell in the rosiglitazone group (mean change from baseline rosiglitazone −1.9%, placebo −0.2%; between-group difference 1.7%, 95% confidence interval 0.6–2.7, $P < 0.01$); lumbar spine bone density fell significantly from baseline values in the rosiglitazone group ($P = 0.02$ *vs.* baseline) but was not significantly different between groups (mean change from baseline rosiglitazone −1.2%, placebo −0.2%; between-group difference 1.0%, 95% confidence interval −0.2–2.3, $P = 0.13$).

Conclusions: Short-term therapy with rosiglitazone exerts detrimental skeletal effects by inhibiting bone formation. Skeletal end points should be included in future long-term studies of thiazolidinedione use. **(*J Clin Endocrinol Metab* 92: 1305–1310, 2007)**

THIAZOLIDINEDIONES ARE insulin-sensitizing agents that are widely prescribed in the management of a variety of clinical conditions characterized by insulin resistance (1, 2). They are agonists of the peroxisome proliferator-activated receptor (PPAR) family of nuclear transcription factors, in particular the PPAR-γ isoform (1). In patients with type 2 diabetes mellitus, their use is associated with significant improvements in glycemic control and serum lipoprotein profile, although their ability to reduce the incidence of vascular events is uncertain (3). At present, thiazolidinediones account for 21% of oral antihyperglycemic drugs used in the United States and 5% in Europe (4). It is estimated that 2 million Americans were prescribed rosiglitazone last year (personal communication, Westun, C., GlaxoSmithKline, New Zealand).

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Abbreviations: BMD, Bone mineral density; βCTX, β-C-terminal telopeptide of type I collagen; P1NP, procollagen type-I N-terminal propeptide; PPAR, peroxisome proliferator-activated receptor.

PPAR-γ is expressed in a number of tissues (1), raising the possibility that drugs that interact with it may induce clinical effects other than insulin sensitization. Prominent among the tissues in which PPAR-γ is expressed is bone. In skeletal tissue, PPAR-γ acts as a molecular switch that regulates the fate of pluripotent mesenchymal stem cells, which have the ability to differentiate into adipocytes or osteoblasts. *In vitro*, PPAR-γ agonists promote adipocyte differentiation in preference to osteoblast differentiation (5–8). There are conflicting reports of the effects of PPAR-γ activation on osteoclastogenesis (9, 10). Haploinsufficiency of the PPAR-γ gene in mice induces a high bone density phenotype characterized by increased rates of osteoblastic bone formation (11, 12), whereas treatment of rodents with PPAR-γ agonists induces bone loss characterized by deficient osteoblast function (12–14). Data from human studies of the skeletal actions of thiazolidinediones are currently available only from an observational study, which reported that female, but not male, diabetic thiazolidinedione users experience accelerated bone loss, compared with nonthiazolidinedione users (15).

Patients with type 2 diabetes may be at increased risk of fragility fractures (16–22). Because PPAR-γ agonists are in-

creasingly frequently used to treat this disease, it is important to determine whether these drugs have adverse effects on the human skeleton. We undertook a randomized, placebo-controlled trial to test the hypothesis that treatment with rosiglitazone would cause adverse skeletal effects in healthy postmenopausal women. The primary objective was to determine the effect of rosiglitazone 8 mg daily on biochemical markers of bone formation over a 14-wk period. Secondary end points were change in markers of bone resorption and bone mineral density.

Subjects and Methods

Participants

Participants were normal postmenopausal women who were more than 5 yr postmenopausal and aged older than 55 yr. They were recruited between January and October 2005. Women with illnesses or receiving therapies likely to affect bone were ineligible, as were those with osteoporosis [bone mineral density (BMD) T score at lumbar spine or total hip ≤ -2.5] and those with any other major systemic disease or contraindications to the use of thiazolidinediones. Subjects were recruited by advertisements seeking healthy postmenopausal women to participate in clinical bone research. Of the 183 women who received study information sheets, 75 attended a screening visit (Fig. 1). Six women met exclusion criteria (one taking estrogen, one taking a bisphosphonate, one taking glucocorticoids, one taking an anticonvulsant, one with cancer, one with primary hyperparathyroidism), and 19 women elected for personal reasons (10 concerned about possible weight gain, two unwilling to undergo blood tests, four with nonexclusionary intercurrent illnesses, three for unstated reasons) not to proceed to randomization.

Among the 50 women randomized, four (two placebo, two rosiglitazone) withdrew during the study. One woman in each group never started study medication (withdrew for personal reasons). One participant in the rosiglitazone group withdrew at 4 wk because of menopausal symptoms, and one participant in the placebo group withdrew after 16 d because of limb paresthesiae. Five women in the rosiglitazone group reported ankle swelling during the study, one of whom took 4 mg daily throughout.

Protocol

A randomized trial, comparing rosiglitazone 8 mg daily (2×4 mg tablets) with placebo over a period of 14 wk was performed. The placebo tablet was similar, but not identical with, the active tablet. Tablets were dispensed into identical opaque containers by a staff member who was not involved in giving study medication to participants. Each container was labeled with the subject's study number and distributed to the participant by another staff member. Subjects took one study tablet daily for the first 2 wk and then two tablets daily for the remainder of the study. Blood samples were collected fasting between 0800 and 1000 h at baseline and 2, 4, 8, and 14 wk. Treatment allocations were randomized by the study statistician, using a variable block size schedule, based on computer-generated random numbers. To ensure masking, only the statistician had access to treatment allocation. All the other study personnel and subjects were blinded to treatment allocation throughout. Only the study statistician saw unblinded data, but he had no contact with study participants. The study was approved by the Auckland Ethics Committee, and written informed consent was provided by each participant. The trial is registered at the Australian Clinical Trials Register (ACTRN 012605000218695; www.actr.org.au).

Measurements

Serum calcium, phosphate, albumin, and total alkaline phosphatase activity were measured on a modular autoanalyzer (Roche, Stockholm, Sweden). 25-Hydroxyvitamin D was measured using a chemiluminescent assay (Nichols, San Juan Capistrano, CA). Intact PTH was measured using an electrochemiluminescence immunoassay (E170; Roche). Serum osteocalcin, serum β-C-terminal telopeptide of type I collagen (βCTX) and serum procollagen type-I N-terminal propeptide (P1NP) were measured using commercially available kits, as previously described (23, 24). Coefficients of variation of these markers are as follows: osteocalcin, 5.5%; βCTX, 5.1%; PINP, 1.9%. Each turnover marker was assayed at the end of the study period in a single batch. Samples were stored at -70 C.

Bone mineral density of the lumbar spine and proximal femur was measured by dual-energy x-ray absorptiometry using a Lunar Prodigy instrument (GE-Lunar, Madison, WI; software version 7.51.008) at baseline and 14 wk. Bone density measurements were performed by two experienced technicians, both of whom are certified by Synarc, the international company that provides bone density oversight for most international osteoporosis drug registration trials. The coefficients of variation for measurement of total hip and lumbar spine bone mineral densities in our laboratory are 1.1 and 1.4%, respectively.

Statistics

The primary end points of the study were the two specific markers of bone formation, osteocalcin and P1NP. The study was therefore de-

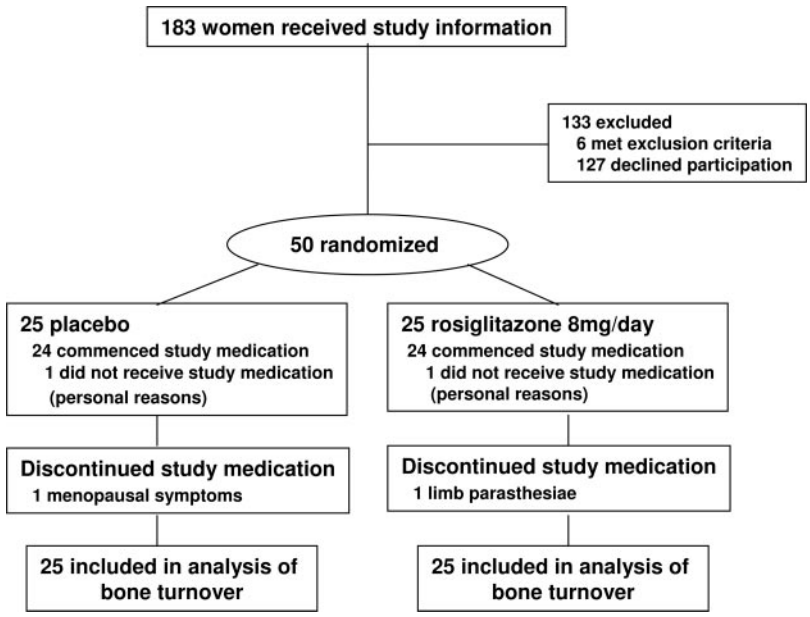

FIG. 1. Flow of subjects through the study.

signed to detect a 1 SD difference between the treatment groups in the change in either of these markers. Because recruitment made allowance for dropouts, the number of completing subjects provides 80% power at the 5% significance level to detect differences of at least 90% of 1 SD between the placebo and rosiglitazone arms. Sample-size calculations were performed using PASS (NCSS and PASS number cruncher statistical systems, Kaysville, UT). Procedures of the statistical analysis system SAS (version 9.2; SAS Institute Inc., Cary, NC) were used for all analyses. All statistical tests were two tailed, and a 5% significance level was maintained throughout. All treatment evaluations were performed on the principle of intention to treat. A mixed-models approach to repeated measures was used to examine the time course of response in treatment and control arms at baseline and at 2, 4, 8 and 14 wk. The correct covariance structure was determined by likelihood ratio test (*i.e.* the first-order autoregression matrix was compared against an unstructured covariance matrix). Maximum likelihood imputation was used to ensure all the randomized patients could be included in the model (25). The assumptions of normality of the dependent variable and residuals were tested by inspection and goodness of fit assessed by maximizing the Akaike information criterion. *P* values for significant main and interaction (treatment by time) effects were constructed using the method of Tukey.

Results

The baseline characteristics of the study subjects are shown in Table 1. At baseline, the only significant difference between the study groups was in serum osteocalcin, which was lower in the rosiglitazone group. Five of 25 subjects in the placebo group and four of 25 subjects in the rosiglitazone group were taking calcium supplements at study inception; in each case the dose was unchanged during the study. No subjects took vitamin D supplements during the study. Compliance with study medication, as assessed by tablet counts, was 97% in the placebo group and 99% in the rosiglitazone group.

The effects of rosiglitazone on markers of bone turnover are shown in Fig. 2. Figure 2, A and B, shows the osteoblast-specific markers P1NP and osteocalcin. Each of these markers of bone formation was stable in the placebo group and declined significantly in the rosiglitazone group. Overall, P1NP declined by 13% in the rosiglitazone group by 4 wk, and this effect was maintained for the remainder of the study (*P* for time × treatment interaction = 0.004). Osteocalcin fell by 8% from baseline values in the rosiglitazone group, and the between-groups difference in this bone formation marker was 10% at the study conclusion (*P* for time × treatment interaction = 0.04). Total serum alkaline phosphatase also declined, by 17%, in the rosiglitazone group and remained stable in the placebo group (mean change +0.01%) (*P* for time × treatment interaction < 0.001). γ-Glutamyl transferase did not change during the study (*P* for time × treatment interaction = 0.11).

TABLE 1. Baseline characteristics of study subjects

Characteristic	Placebo	Rosiglitazone
n	25	25
Age (yr)	68 (8)	67 (9)
Weight (kg)	70 (13)	69 (14)
Height (cm)	160 (5)	161 (6)
Years since menopause	18 (9)	17 (9)
Dietary calcium intake (mg/d)	700 (340)	670 (340)
25-hydroxyvitamin D (μg/liter)	32 (14)	31 (12)
P1NP (μg/liter)	51 (17)	48 (22)
Osteocalcin (μg/liter)	27 (10)	22 (8)[a]
βCTX (ng/liter)	382 (145)	358 (149)
Lumbar spine BMD (g/cm^2)	1.13 (0.13)	1.18 (0.26)
Total hip BMD (g/cm^2)	0.96 (0.10)	0.99 (0.14)

Data are mean (SD) or number of subjects. Biochemical analytes are measured in serum. To convert 25-hydroxyvitamin D values to nanomoles per liter, multiply by 2.5.

[a] $P < 0.05$ *vs.* placebo.

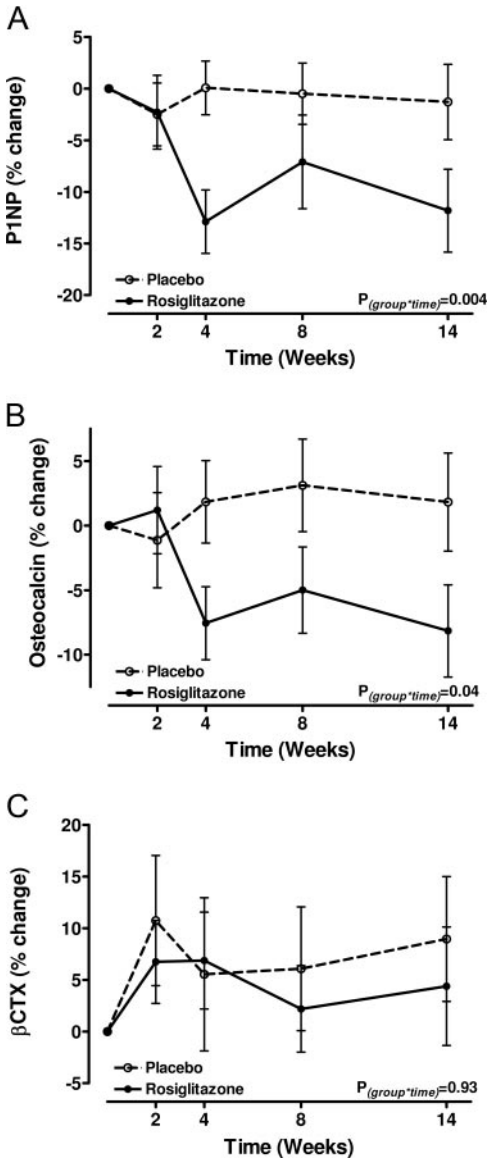

FIG. 2. The effects of rosiglitazone or placebo on markers of bone turnover in normal postmenopausal women. A, Serum P1NP. B, Serum osteocalcin. C, βCTX *P* (group × time) is the *P* value for the time-treatment interaction. Data are mean ± SEM percent change from baseline.

In contrast to the bone formation markers, levels of serum βCTX, a marker of bone resorption, did not change in response to rosiglitazone (*P* for time × treatment interaction = 0.9, Fig. 2C).

There were no differences between the groups in the levels of serum calcium, phosphate, and PTH (Table 2). Mean values of each of these variables were within the normal range throughout the study.

The changes in bone density are shown in Fig. 3. Total hip

TABLE 2. Serum biochemistry in study subjects

Variable	Placebo			Rosiglitazone		
	Baseline	4 wk	14 wk	Baseline	4 wk	14 wk
Serum calcium (mg/dl)	9.0 (0.02)	9.0 (0.03)	9.1 (0.03)	8.9 (0.03)	8.8 (0.02)	8.8 (0.03)
Serum phosphate (mg/dl)	3.8 (0.4)	3.9 (0.4)	3.9 (0.5)	3.7 (0.4)	3.9 (0.4)	3.9 (0.5)
Plasma PTH (pg/ml)	42 (13)	43 (12)	44 (17)	39 (11)	40 (10)	36 (9)

Data are mean (SD). There were no differences between the groups in the change from baseline values in any of the variables shown. To convert serum calcium to millimoles per liter, multiply by 0.25; to convert serum phosphate to millimoles per liter, multiply by 0.32; to convert PTH to picomoles per liter, multiply by 0.11.

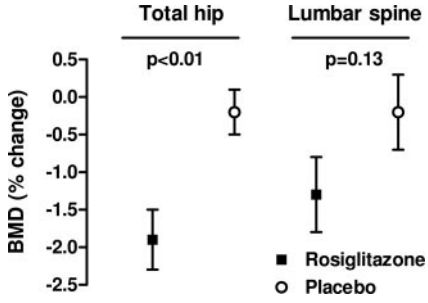

FIG. 3. The effect of rosiglitazone or placebo on BMD in normal postmenopausal women. *P* values refer to comparisons between groups in the percent change from baseline at each indicated skeletal site. Data are mean ± SEM percent change from baseline.

bone density declined by a greater amount in the rosiglitazone group than the placebo group [mean (SD) change rosiglitazone −1.9 (2.0)%, placebo −0.2 (1.6)%, between-groups difference 1.7%, 95% confidence interval 0.6–2.7, $P = 0.003$]. Lumbar spine bone density fell significantly from baseline values in the rosiglitazone group ($P = 0.02$ *vs.* baseline) and remained stable in the placebo group ($P = 0.7$ *vs.* baseline) but was not different between groups [mean (SD) change rosiglitazone −1.2 (2.1)%, placebo −0.2 (2.1)%, between-groups difference 1.0%, 95% confidence interval −0.2–2.3, $P = 0.13$]. As expected, body weight tended to increase in the rosiglitazone group (mean change rosiglitazone +0.7 kg; placebo −0.8 kg, *P* for between-groups comparison in change from baseline = 0.07). Adjusting the bone density data for change in body weight, the baseline osteocalcin level, or both variables did not change the results.

Discussion

This study demonstrates that short-term therapy with rosiglitazone, a commonly prescribed PPAR-γ agonist, inhibits bone formation and accelerates bone loss in healthy postmenopausal women. These data are consistent with those from *in vitro* and animal studies demonstrating that PPAR-γ signaling negatively regulates osteoblast function (bone formation) and bone mass (7, 8, 11, 13, 14). The pattern of alteration of bone remodeling that we observed in response to rosiglitazone is similar to that seen after the initiation of glucocorticoid therapy (26). The uncoupling of bone formation from resorption by glucocorticoids is accompanied by early and rapid bone loss and an increased risk of fragility fractures (27). Our data suggest that rosiglitazone may also promote rapid bone loss; longer-term studies are needed to determine whether the rate of loss we observed is sustained. Because patients with type 2 diabetes may have an increased risk of fragility fractures (16–20), the possibility that one of the therapies commonly used to treat the disease may be increasing that risk is a cause for concern. The increasing use of thiazolidinediones in other clinical conditions characterized by insulin resistance (28, 29), including impaired glucose tolerance (30), is a further reason to fully characterize their long-term skeletal effects. We therefore suggest that skeletal safety end points should be added to existing and planned randomized trials of PPAR-γ agonists so that the skeletal effects of thiazolidinediones can be studied over a longer period.

Although preclinical studies have consistently reported that rosiglitazone impairs osteoblast function (13, 14, 31, 32), conflicting *in vitro* data exist as to whether PPAR-γ signaling affects osteoclastogenesis (7, 9, 10). Our data suggest that PPAR-γ agonists do not influence bone resorption *in vivo*, a finding consistent with those of *in vivo* studies in rodents (11, 13, 14). The limited preclinical data that are available on the skeletal effects of pioglitazone, the other commonly prescribed thiazolidinedione, suggest that it has comparable actions with those of rosiglitazone (33, 34). Whether there is a class effect of thiazolidinediones on skeletal homeostasis is uncertain, with recent preclinical studies of new compounds reporting both adverse (35) and neutral (36) effects in rodent models.

Currently there are few data available on the skeletal actions of thiazolidinediones in humans. Uncontrolled studies of Japanese subjects with type 2 diabetes treated with troglitazone, a PPAR-γ agonist no longer in clinical use, reported significant reductions in markers of both bone formation and resorption after 1 month, but values returned to baseline by 1 yr (37, 38). More recently an analysis of the small number (n = 69) of diabetic subjects taking thiazolidinediones (pioglitazone, troglitazone, and rosiglitazone) in the Health, Aging, and Body Composition observational study reported accelerated bone loss in over 4 yr in women but not men (15). After our manuscript was submitted, Kahn *et al.* (39) reported a higher incidence of fractures, detected as adverse events, in female diabetic subjects randomized to receive rosiglitazone, compared with those randomized to receive either metformin or glyburide, during a 4 yr study of glycemic durability of oral monotherapies. Our findings provide rigorous evidence for a detrimental effect of PPAR-γ agonists on the postmenopausal female skeleton. Whether there is a gender difference in the skeletal response to thiazolidinediones can be determined only by a randomized, controlled trial in men.

The mechanism(s) by which rosiglitazone alters bone remodeling likely involves direct effects on osteoblast development and function, but the possibility of indirect skeletal

actions also exists. Adipose tissue is a target for PPAR-γ agonists, and some adipokines influence bone cell function. Thiazolidinediones may decrease circulating levels of leptin (38), the peripheral actions of which include osteoblast anabolism (40). The insulin-sensitizing actions of PPAR-γ agonists lower circulating levels of insulin (1) and therefore are likely to reduce levels of the cosecreted pancreatic β-cell peptide amylin, each of which is anabolic to osteoblasts (41, 42).

A theoretical limitation of our study is the possibility that dual-energy x-ray absorptiometry may underestimate bone density in rosiglitazone-treated subjects because of changes in bone marrow adiposity. We think this unlikely because, although it is not known whether rosiglitazone increases marrow fat in humans, 30-fold higher doses (by body weight) of drug than those used in our study do not increase marrow fat in rodents (13), and dual-energy x-ray absorptiometry accurately measures bone density *in vivo*, as corroborated by histomorphometry and/or microcomputed tomography, when marrow adiposity is known to be either increased (31, 36) or absent (43).

Limitations of the present study are its short duration and the healthy volunteer study population. An advantage of studying healthy subjects is that it allows an assessment of the effects of rosiglitazone on bone metabolism, independent of any confounding introduced by improvements in the metabolic control of diabetes mellitus (44). Furthermore, because the indications for use of thiazolidinediones are expanding to include individuals with insulin resistance (30), assessment of their bone effects outside the context of a specific pathological state is appropriate. The short duration of the study was necessary because the hypothesis was one of harm, and the study participants were normal volunteers who would not be expected to benefit from the intervention. We believe that the 14-wk study duration was adequate to provide proof of principle that thiazolidinediones impact adversely on the human skeleton, without exposing the subjects to a significant risk of long-term skeletal harm. Longer-term studies are clearly necessary, but these would best be undertaken in study populations that might reasonably be expected to derive some benefit from thiazolidinedione use, such as people with type 2 diabetes and/or impaired glucose tolerance.

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