EDITORIAL (SEE YATURU ET AL., P. 1574)

Thiazolidinedione Therapy Gets Complicated

Is bone loss the price of improved insulin resistance?

An escalating number of recent publications suggest that the thiazolidinedione (TZD) medications may have a negative effect on the skeleton. The manufacturers of the two currently available TZDs, rosiglitazone and pioglitazone, have both issued letters to health care providers, warning that these medications may cause an increased risk of fracture in women (1,2). TZDs improve insulin sensitivity and are widely prescribed for type 2 diabetes, but we are just beginning to understand their clinical effects on bone.

In December 2006, the ADOPT trial reported a higher risk of fractures in diabetic women randomized to rosiglitazone than in women randomized to metformin or glyburide (3). The ADOPT trial followed 4,360 (42% women) participants with a mean age of 57 years for a median of 4 years. The primary outcome was time to monotherapy failure as determined by fasting glucose. An imbalance in fracture rates was identified in a final review of adverse event reports. The proportion of women reporting a fracture was 9.3% for rosiglitazone, 5.1% for metformin, and 3.5% for glyburide, corresponding to an approximate relative risk (RR) of 2.18 (95% CI 1.52–3.13) for rosiglitazone versus the other treatments combined. Among male participants, 89 reported a fracture, distributed similarly across treatments (rosiglitazone 3.9%, metformin 3.4%, and glyburide 3.3%), corresponding to an approximate RR of 1.18 (0.77–1.80), for rosiglitazone versus the other treatments combined.

Pioglitazone, the other currently available TZD, may also have negative skeletal effects. In March 2007, Takeda (2) reported increased fracture risk in women, but not men, using pioglitazone, based on an analysis of their clinical trial database, including 24,000 person-years of follow-up. Among women, fracture incidence was 1.9 per 100 person-years for pioglitazone and 1.1 per 100 person-years for those using placebo or another active drug. The incidence for men was not reported but did not differ statistically between the pioglitazone and comparison groups.

Results of a randomized controlled trial, published electronically in January 2007, added to the evidence that TZDs have negative effects on the skeleton. In a trial that enrolled 50 postmenopausal women without diabetes or osteoporosis, Grey et al. (4) reported bone loss with rosiglitazone. After 14 weeks of treatment (8 mg/day), total hip bone density decreased significantly in the rosiglitazone group (−1.9% rosiglitazone vs. −0.2% placebo). Markers of bone formation were also reduced (−8 to −13%), while no change was seen in resorption markers. Although these results were found in women without diabetes, the fracture results cited above suggest that the findings apply to those with diabetes as well. In addition, we have shown that older diabetic women taking any TZD (rosiglitazone, pioglitazone, and troglitazone) in the observational Health, Aging and Body Composition (Health ABC) study had an increased rate of bone loss (5).

In this issue Yaturu et al. (6) provide evidence that rosiglitazone may also cause bone loss in older men. This observational study compared changes in bone density over an average of 16 months in 160 older (average age 68 years) men with diabetes, 32 using rosiglitazone and 128 who had not used any TZD. Those using rosiglitazone lost bone more rapidly. In unadjusted models, the difference in annual bone loss was −1.05% at the total hip, −1.02% at the femoral neck, and −1.24% at the spine. This study has important limitations, including its observational design and the lack of adjustment for potential confounders. The only other data available on men is from the Health ABC observational study, reporting a modest increase in bone loss that was not statistically significant (5). Older diabetic men using any TZD had additional annual bone loss of −0.25% (95% CI −1.10 to 0.60) at the spine and −0.19% (−0.61 to 0.22) at the total hip, compared with bone loss among diabetic men without TZD use. Changes in bone with TZD use in men have not been investigated in a randomized clinical trial. Thus, our knowledge of the effects of TZDs on bone in men is quite limited. The results reported by Yaturu et al. (6) indicate that further study in men is warranted.

Studies with rodent models have found increased bone loss with rosiglitazone and pioglitazone treatment and suggest that the mechanism is decreased osteoblast function (7–10). TZDs activate the nuclear hormone receptor, peroxisome proliferator–activated receptor-γ (PPAR-γ), improving insulin sensitivity. PPAR-γ activation also influences the lineage allocation of mesenchymal stem cells (MSCs) in the bone marrow. With rosiglitazone treatment, MSCs are increasingly allocated toward adipocytes, and differentiation toward osteoblasts is decreased (11). The effect of PPAR-γ activation on osteoclasts has not been elucidated, with some studies finding no effect (7–9) but others finding increased bone resorption (12). In one animal model, ovariectomized, but not intact, rats experienced bone loss with rosiglitazone treatment, suggesting that low levels of endogenous estrogen may enhance the negative effect of rosiglitazone on bone (12). This effect modification with estrogen levels is one possible explanation for the sex differences seen in fracture rates with TZD therapy since postmenopausal women tend to have lower endogenous estrogen levels than men of a similar age.

The short trial by Grey et al. (4) found 1.7% more bone loss in the rosiglitazone-treated group compared with placebo over just 14 weeks. If this rate of bone loss continued, the additional loss with rosiglitazone therapy would be >6% per year. However, in both the Health ABC study and the study in this issue by Yaturu et al., the additional annual bone loss for women or men attributable to TZD use was considerably lower, on the order of ≤1.2% per year for the hip and spine (5,6). These differences might be due to

different study population characteristics and study design; however, they do raise the question of the overall magnitude of bone loss that might occur with TZD therapy. The evidence from bone markers, bone density scans, and fracture risk suggests that the TZDs cause clinically important bone loss, at least in postmenopausal women, but the degree of bone loss remains a question.

Longer-term clinical trials are needed to clarify the extent of bone loss potentially related to TZD therapy, to determine whether men are also susceptible, and to identify the effects in younger adults. Additional work using animal and in vitro models will also be needed to elucidate the underlying mechanisms by which TZDs interact with the skeleton.

More investigation is needed; however, at this time, health care providers should be made aware of the potential for increased bone loss and fracture risk with TZD use. In ADOPT, where the mean age was 57 years, the annual fracture rate among women using rosiglitazone was 2.7%, about double the 1.3% rate in the glyburide group. The absolute increase in fracture risk will vary depending on age, bone density, and other risk factors for fracture. For example, in an older cohort of diabetic women (average age 72 years), the reported fracture rate was 4.3% (13). If the same RR observed in the ADOPT trial holds and this rate doubles with TZD use, then the absolute fracture rate would increase to ~8–9%. To provide perspective, this relative increase in fracture risk is similar to what has been observed with a 1 SD decrease in bone density, i.e., a *T* score decrease of one point. These estimates are necessarily very approximate, given the limited research on TZDs and fracture, but provide a sense of the possible increase in fracture risk that can be weighed against the proven benefits of TZDs in treating diabetes.

The data to date are probably not sufficient to recommend widespread osteoporosis screening for all patients being considered for TZD therapy or those already on a TZD. However, older postmenopausal women are at the greatest risk for fracture and also the group for whom data on the adverse skeletal effects of TZD therapy are the most consistent. For postmenopausal women using or starting TZD therapy, a conservative approach to osteoporosis screening would seem warranted, initiating screening for low bone density at the time of menopause and instituting osteoporosis treatment in women found to be at increased risk for fracture.

The value of screening bone density testing in younger individuals and men is not as well established. Currently, these patients are selected for testing based on clinical risk factors or the presence of a secondary cause of bone loss. The study in this issue by Yaturu et al. (6) is the first to suggest that men may also be susceptible to bone loss associated with TZD therapy. At this time, it would seem prudent to consider the presence of TZD therapy when developing an overall impression of fracture risk for each patient and determining whether screening bone density testing is necessary. Nutrition and lifestyle recommendations for bone health should be implemented in all patients and specific osteoporosis therapy initiated in those individuals who appear to be at increased fracture risk based on clinical risk factors and the results of bone density testing. The benefits of TZD therapy to improve glycemic control and prevent complications of diabetes are well established. Further data are needed to determine the magnitude of the potential skeletal effects and the overall risk benefit ratio for individuals with diabetes.

ANN V. SCHWARTZ, PHD[1]
DEBORAH E. SELLMEYER, MD[2]

From the [1]Division of Epidemiology and Biostatistics, University of California San Francisco, San Francisco, California; and the [2]Division of Endocrinology and Metabolism, University of California San Francisco, San Francisco, California.

Address correspondence to Ann V. Schwartz, PhD, 185 Berry St., Suite 5700, San Francisco, CA 94107. E-mail: aschwartz@psg.ucsf.edu.

A.V.S. has been a consultant for GlaxoSmithKline.

DOI: 10.2337/dc07-0554

References

1. GlaxoSmithKline (GSK): Clinical trial observation of an increased incidence of fractures in female patients who received long-term treatment with Avandia (rosiglitazone maleate) tablets for type 2 diabetes mellitus (Letter to Health Care Providers), February 2007. Available from www.fda.gov/MedWatch/safety/2007/Avandia_GSK_Ltr.pdf. Accessed 15 March 2007
2. Takeda: Observation of an increased incidence of fractures in female patients who received long-term treatment with ACTOS (pioglitazone HCl) tablets for type 2 diabetes mellitus (Letter to Health Care Providers), March 2007. Available from www.fda.gov/medwatch/safety/2007/Actosmar0807.pdf. Accessed 19 March 2007
3. Kahn SE, Haffner SM, Heise MA, Herman WH, Holman RR, Jones NP, Kravitz BG, Lachin JM, O'Neill MC, Zinman B, Viberti G: Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. *N Engl J Med* 355:2427–2443, 2006
4. Grey A, Bolland M, Gamble G, Wattie D, Horne A, Davidson J, Reid IR: The peroxisome-proliferator-activated receptor-gamma agonist rosiglitazone decreases bone formation and bone mineral density in healthy postmenopausal women: a randomized, controlled trial. *J Clin Endocrinol Metab* 92:1305–1310, 2007
5. Schwartz AV, Sellmeyer DE, Vittinghoff E, Palermo L, Lecka-Czernik B, Feingold KR, Strotmeyer ES, Resnick HE, Carbone L, Beamer BA, Park SW, Lane NE, Harris TB, Cummings SR: Thiazolidinedione use and bone loss in older diabetic adults. *J Clin Endocrinol Metab* 91:3349–3354, 2006
6. Yaturu S, Bryant B, Jain S: Thiazolidinediones treatment decreases bone mineral density in type 2 diabetic men. *Diabetes Care* 2007 Mar 15 [Epub ahead of print]
7. Rzonca SO, Suva LJ, Gaddy D, Montague DC, Lecka-Czernik B: Bone is a target for the antidiabetic compound rosiglitazone. *Endocrinology* 145:401–406, 2004
8. Soroceanu MA, Miao D, Bai XY, Su H, Goltzman D, Karaplis AC: Rosiglitazone impacts negatively on bone by promoting osteoblast/osteocyte apoptosis. *J Endocrinol* 183:203–216, 2004
9. Ali AA, Weinstein RS, Stewart SA, Parfitt AM, Manolagas SC, Jilka RL: Rosiglitazone causes bone loss in mice by suppressing osteoblast differentiation and bone formation. *Endocrinology* 146:1226–1235, 2005
10. Syversen U, Stunes A, Gustafsson B, Waarsing J, van Leeuwen H, Weinans H, Westbroek I: The PPAR gamma agonist fenofibrate prevents bone loss, while the PPAR alpha agonist pioglitazone exaggerates bone loss in ovarectomized rats (Abstract). *J Bone Miner Res* 21 (Suppl. 1):S216, 2006
11. Lecka-Czernik B, Gubrij I, Moerman EJ, Kajkenova O, Lipschitz DA, Manolagas SC, Jilka RL: Inhibition of Osf2/Cbfa1 expression and terminal osteoblast differentiation by PPARgamma2. *J Cell Biochem* 74:357–371, 1999
12. Sottile V, Seuwen K, Kneissel M: Enhanced marrow adipogenesis and bone resorption in estrogen-deprived rats treated with the PPARgamma agonist BRL49653 (rosiglitazone). *Calcif Tissue Int* 75:329–337, 2004
13. Schwartz AV, Sellmeyer DE, Ensrud KE, Cauley JA, Tabor HK, Schreiner PJ, Jamal SA, Black DM, Cummings SR: Older women with diabetes have an increased risk of fracture: a prospective study. *J Clin Endocrinol Metab* 86:32–38, 2001