

Three Perspectives on Thiazolidine and Bone Health



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ACRONYMS in this Article

- T2DM** = type 2 diabetes mellitus
- TZD** = thiazolidinediones
- PPAR** = peroxisome proliferator-activated receptor
- SPPARM** = selective PPAR γ modulator
- BMD** = bone mineral density

Introduction

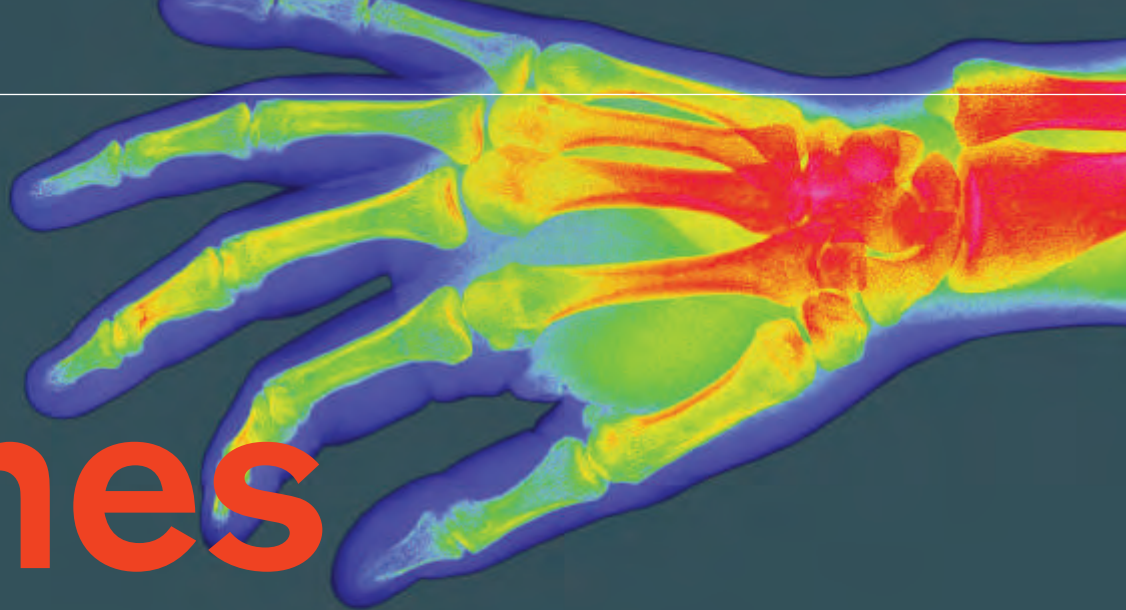
Recent epidemiological studies have suggested that skeletal fragility is increased in T2DM. TZDs or insulin-sensitizing drugs that activate the gamma isoform of the PPAR family of nuclear transcription factors—are commonly used in T2DM treatment. In vitro studies demonstrate that TZDs inhibit osteoblast differentiation and promote osteoclastogenesis, and that administering TZDs to rodents decreases bone mass. Recent data from clinical studies show impaired bone formation, accelerated bone loss, and higher fracture incidence in humans exposed to TZDs. Thus, use of these drugs exacerbates skeletal fragility in a population already at increased risk of fracture. Further examination of the molecular mechanisms by which PPAR γ affects bone cell function is

likely to significantly advance our understanding of skeletal physiology, and facilitate development of selective PPAR γ modulators that do not harm the skeleton. Further clinical research is required to elucidate the magnitude and mechanism(s) of TZD-induced skeletal toxicity in humans and to determine which interventions may abrogate this effect.

Basic Scientist Perspective

- TZDs, a class of insulin-sensitizing drugs, cause bone loss in mice and rats.
- TZDs function as agonists for PPAR γ .
- PPAR γ activation by TZDs suppresses osteoblast formation and promotes osteoclast differentiation.
- Data on the effects of PPAR γ polymorphisms on BMD are scant.
- Mechanistic information will foster development of SPPARMs that retain insulin-sensitizing benefits without the concurrent bone-loss effect.

diones



TZDs (rosiglitazone and pioglitazone) are a class of insulin-sensitizing drugs used in T2DM treatment. Among patients with diabetes in clinical trials, long-term use of TZDs has been reported to increase fracture rates.^{1,2} Furthermore, TZD treatment has been shown to cause bone loss in both mice and rats.³⁻⁶ Therefore, it is important to understand the cellular and molecular mechanisms underlying TZDs' action in bone. Such knowledge should foster the development of SPPARMs that can retain the insulin-sensitizing benefits but dampen the detrimental bone effects.

The Yin and Yang in Bone: Osteoblast and Osteoclast

Bone is a dynamic tissue that undergoes constant remodeling by balancing osteoblast-mediated bone formation and osteoclast-mediated bone resorption. This remodeling is regulated by numerous factors, including nutritional, hormonal, mechanical, and immunological signals. When bone resorption outpaces bone formation, osteoporosis occurs. With the aging of society, more than 10 million Americans are suffering from osteoporosis. The disease is responsible for approximately 1.5 million fractures and 40,000 deaths per year. The two main cell types in bone are of distinct developmental origins: osteoblasts have a mesenchymal lineage, whereas osteoclasts are of hematopoietic lineage. TZDs have been shown to both inhibit osteoblast differentiation^{7,8} and to stimulate osteoclast differentiation,^{9,10} and thus act as a double-edged sword in promoting bone loss.

TZDs Target PPAR γ , a Central Metabolic Regulator

TZDs function as agonists for PPAR γ , which regulates many processes, including insulin action, adipocyte differentiation, lipid metabolism, inflammation, atheroscle-

rosis, kidney function, and cancer. Emerging evidence suggests that PPAR γ also plays important roles in skeleton and mineral metabolism. On the one hand, PPAR γ activation by TZDs suppresses osteoblast differentiation from mesenchymal stem cells by promoting adipocyte differentiation. PPAR γ heterozygous mice display high bone mass due to increased osteoblast number and bone formation.⁷ On the other hand, recent evidence shows that PPAR γ activation by rosiglitazone has an independent role in promoting osteoclast differentiation from hematopoietic progenitor cells in a receptor-dependent manner.¹⁰ Reciprocally, loss of PPAR γ function in mouse hematopoietic cells causes osteopetrosis characterized by increased bone mass, reduced medullary cavity space, altered bone remodeling, and extramedullary hematopoiesis in the spleen.¹⁰ Together, these findings suggest that TZDs might mediate bone loss by activating PPAR γ in both mesenchymal and hematopoietic progenitor cells, decreasing bone formation, and increasing bone resorption. Future studies will be required to determine if TZDs' "bone-consuming" is influenced by either age or sex. In addition, it is important to determine if TZDs affect bone through systemic factors from the central nervous system and other metabolically active organs such as fat, muscle, and liver.

Do Natural PPAR γ Mutations in Humans Affect Bone Health?

Mouse genetic studies have provided compelling evidence that PPAR γ is required for normal skeletal development and metabolism. In humans, an important question needs to be answered: Do naturally occurring PPAR γ mutations or single nucleotide polymorphisms affect bone health? Several hu-

man PPAR γ mutations have been linked to lipodystrophy, insulin resistance, or colon cancer.¹¹ Follow-up studies on these populations will shed light on how PPAR γ polymorphisms affect skeletal mass and mineral density, as well as hematopoiesis in the bone marrow, which is regulated by the bone environment. These studies will not only elucidate PPAR γ 's role in human bone health, but will also provide molecular insights into identifying the critical amino acid residues in PPAR γ required for bone regulation.

SPPARMs: Can the Insulin Sensitizing Benefit of PPAR γ Activation Be Separated from the Bone Loss Harm?

PPAR γ regulates transcription in a cell type- and gene-specific manner. This specificity is currently believed to be largely based on the unique protein network in each cell type, and the corepressors/coactivators required for each individual target gene. Detailed examination of the mechanisms underlying the distinction between PPAR γ regulation of insulin sensitivity and of bone cell differentiation will identify the features that permit separation of these two actions. Thus, it should be possible to develop bone-sparing TZDs that activate only the PPAR γ target genes required for the beneficial insulin-sensitizing effect, while avoiding activation of the PPAR γ target genes responsible for the detrimental bone-loss effect.¹²

Clinical Scientist Perspective

- Current evidence suggests that TZDs decrease bone formation and bone density, and increase fracture incidence.
- The magnitude, mechanism, and reversibility of TZDs' effects on bone turnover and density are unknown.
- Very few data are available on TZDs' skeletal effects in men.
- Whether TZDs raise the risk of fractures of the axial skeleton is unknown.
- No data exist yet on how osteoporosis therapies affect TZD-induced skeletal disease.
- Clinically available TZDs—rosiglitazone and pioglitazone—exert adverse influences on skeletal health, at least in women. Uncertainties remain that need to be tackled with some urgency.

Evidence suggests that the clinically available TZDs—rosiglitazone and pioglitazone—exert adverse influences on skeletal health, at least in women. However, a number of uncertainties remain that need to be tackled with some urgency by clinical researchers.

Class Effect on the Skeleton?

Most of the currently available evidence of TZD skeletal toxicity has come from rosiglitazone studies; relatively few

data exist on the skeletal effects of pioglitazone.¹ Recent concerns about rosiglitazone's cardiovascular safety would suggest that pioglitazone use in T2DM patients will increase, so we urgently need clinical studies to evaluate its skeletal effects. Given the in vitro evidence of PPAR γ agonists' ligand-specific effects on skeletal tissue,² any TZD that is developed for clinical use should be evaluated for skeletal toxicity.

Magnitude and Mechanism of Skeletal Effects

Currently, BMD data are available only from short-term studies (3–4 months) of TZDs in humans. We do not know the magnitude of the TZD-induced decrement in BMD, or whether the effect is reversible after treatment stops. Longer term, controlled studies that measure BMD are urgently needed, given the reported association of TZDs and fractures (see below).^{6–9}

In vivo, TZDs decrease bone formation in rodents and humans.¹ Thus far, studies in humans have not demonstrated TZDs' effects on bone resorption. However, evidence from preclinical studies that PPAR γ signaling regulates osteoclastogenesis are sufficient to mandate careful evaluation of this possibility in future clinical studies.^{3, 4} Such mechanistic information will be important in the design of clinical trials aimed at preventing TZD-induced bone loss.

Future clinical studies should also consider TZDs' potential effects on bone marrow adiposity in humans. Evidence is building for a reciprocal relationship between marrow adiposity and osteoblastogenesis/bone formation.⁵ In rodents, high doses of TZDs increase marrow adiposity, providing a potential explanation for impaired bone formation. It is not known whether the clinically applied doses of these drugs alter marrow adiposity in humans.

Are Skeletal Effects Sex-Specific?

Fracture data from TZD trial adverse events reports suggest an increased incidence of fracture only in women.^{6–8} However, an observational study has reported accelerated bone loss in male TZD users,⁹ and a number of the preclinical studies that demonstrated adverse TZD effects were carried out in male animals. It is therefore important to carefully examine how TZDs affect the male skeleton.

Preferential Cortical Bone Loss Linked to TZDs?

The excess of fractures detected in TZD users was concentrated in the appendicular skeleton, suggesting that TZDs induce a region-specific or predominantly cortical bone loss. However, we must realize that given the demographics of the populations enrolled in these studies, distal limb fractures would be expected to be most common.¹⁰ Very few hip fractures were reported in these studies, and no data are available on vertebral fractures. It is therefore premature to conclude that "classical" osteoporotic fractures are not increased in TZD users.

Treatments to Abrogate TZD-Induced Bone Loss

Currently there are no data showing the effects of osteoporosis treatments on TZD-induced bone loss. De-

signing studies for this will be helped as research elucidates the mechanism and magnitude of TZD-induced bone loss, as discussed above. The current clinical trial data suggest that TZDs act primarily to decrease bone formation in humans. Pharmacologic agents that increase bone formation are therefore attractive drugs to study in the prevention of TZD-induced bone loss; however, only one such agent is currently available, and the prohibitive cost of intermittent parathyroid hormone therapy precludes its widespread use. Importantly, potent bisphosphonates are effective in preventing and treating glucocorticoid-induced bone loss, which results primarily from a decline in bone formation.¹¹

Unresolved Questions in TZD-Induced Skeletal Toxicity

There is an urgent need for carefully controlled long-term clinical studies of TZDs' effects on bone turnover and BMD. These findings are important to the design of adequately powered interventional studies of TZD-induced bone loss. They should include both men and women across a range of ages, given the increasing frequency of T2DM in young adults and evidence from animal studies that TZDs' skeletal effects may be age-dependent.⁴

Studying TZDs' impact on fractures is more difficult because it is clearly unethical to design a clinical trial with fracture as the primary end point if the hypothesis is one of harm. Nonetheless, skeletal end points, including fracture, should be included in any current or planned randomized, controlled trial of a TZD.

Analysis of observational databases might ultimately prove to be the most fruitful means of studying fracture risk in TZD users. In existing databases with adequate fracture or even BMD data, the numbers may be too low to allow informative analyses, but as these databases mature, important information is likely to emerge.

Clinician Perspective

- Postmenopausal women with T2DM who are treated with TZDs appear to have an increased risk of distal limb fractures.
- Men and premenopausal women with T2DM have not been shown to have an elevated risk of any type of fracture when treated with TZDs, but men have been shown to lose bone density.
- The clinical significance of heightened risk of distal limb fracture in postmenopausal women and bone loss in men with T2DM treated with TZDs is not yet certain.
- No clinical trials have yet been done to show reduction in fractures or bone loss with osteoporosis drugs in T2DM patients treated with TZDs.
- Given the current lack of clinical knowledge, caution is advised when selecting T2DM patients for treatment with TZDs.

TZDs Increase Risk of Distal Limb Fracture in Postmenopausal Women with T2DM

A variety of observational studies have shown that patients with T2DM are at heightened risk of fracture. Recent clinical trials and database reviews of patients treated with TZDs have shown an increased risk of distal appendicular skeletal fractures in postmenopausal women with T2DM.¹⁻⁴ These studies must somehow be reconciled with the recent report that impaired glucose tolerance is associated with decreased risk for fractures in middle-aged adults with T2DM.⁵

In the large, randomized, double-blind, parallel group study titled "A Diabetes Outcome Progression Trial" (ADOPT),¹⁻³ investigators compared the durability of the treatment effect of rosiglitazone, metformin, or glyburide on glycemic control over 4 years in 4,360 patients aged 30 to 75 years (median, 57 years; 42% women) with recently diagnosed T2DM. Final review of the adverse events reports in the trial showed that 9.3% of women treated with rosiglitazone had fractures compared to 5.1% of women on metformin and 3.5% of women on glyburide. The relative risk of fracture in women taking rosiglitazone compared to the other treatments was 2.18 (95% CI, 1.52-3.13). Similar analysis for men showed no difference between the treatment groups. Fractures of the upper arm, hand, or foot were more common in postmenopausal women in the rosiglitazone group than either of the comparator arms.

Pioglitazone elevated the risk of distal limb fractures in a large manufacturer-led review comparing 8,157 T2DM patients treated with pioglitazone to 7,442 patients treated with comparator drugs for up to 3.5 years, with a total of just less than 12,000 patient-years of exposure in each group.⁴⁻⁵ Among women taking pioglitazone, 2.6% experienced at least one fracture compared with only 1.7% of women on placebo. The incidence of fracture in the pioglitazone group was 1.9 fractures/100 patient-years compared with 1.0 fractures/100 patient-years in the placebo group. Most fractures were of the distal upper and lower limbs, with a few of the hip and spine.

The reported pattern of excess limb fractures, but not increased traditional osteoporotic vertebral or hip fractures, suggests that TZDs may preferentially affect cortical bone rather than trabecular bone. Distal limb non-vertebral fractures are the most common type of fracture expected with these study populations' demographics.

Whether other hypoglycemic agents used to treat diabetes also raise fracture risk is not yet clear. One study showed no effect from metformin when taken at the time of fracture, but increased fracture risk in men only with insulin therapy taken at the time of fracture.⁶

TZDs Undermine BMD in Short-Term Human Studies

A 14-week study of rosiglitazone in 50 postmenopausal women without T2DM or osteoporosis showed total hip bone loss of 1.9% compared to 0.2% in the placebo group.⁷ In a more recent study, men treated with TZDs ex-

perienced more bone loss.⁸ Neither trial was long enough to document the final magnitude or time course of bone loss. An observational study showed that older diabetic women treated with TZDs also had increased bone loss.⁹

TZDs Decrease Markers of Bone Formation in Short-term Human Studies

TZDs have been shown to reduce bone formation in normal humans without T2DM.¹⁰ No human study has yet shown TZD bone resorption effects. If TZDs primarily decrease bone formation by directing osteoblast precursors toward the adipocyte lineage, their effect on fractures would likely not be limited to postmenopausal women.

Preventing Fractures in T2DM

When considering TZDs for patients with T2DM, physicians must be aware that postmenopausal women treated with these medications are at mildly heightened risk for distal appendicular fractures and that older men may experience bone loss. It might be prudent to avoid TZD treatment in postmenopausal women with osteoporosis at high risk of fracture and in older men.

In patients where TZD treatment is highly desirable, providing adequate calcium and vitamin D supplementation and adequate exercise might help minimize TZDs' skeletal impact. Measures to avoid falls or trauma should help reduce the risk of limb and other fractures.

If bone formation reduction is TZDs' primary pathophysiological effect on bone, an anabolic agent would be the most likely drug to improve bone density and decrease fractures. If bone resorption is normally maintained in the setting of decreased bone formation, antiresorptive drugs may also help in patients treated with TZDs. Unfortunately, no clinical trial data from either approach exist to guide therapy. For now, the best strategy may be to use caution when prescribing TZDs to postmenopausal women with T2DM and osteoporosis at high risk for fracture, to women at high risk of falling, and to older men. ■

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