REVIEW ARTICLE

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Risk of Fractures with Glitazones

A Critical Review of the Evidence to Date

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Abstract

The insulin-sensitizing thiazolidinediones (commonly known as glitazones) are an important and widely prescribed class of antidiabetic agents. Glitazones exert their action through activation of proliferator-activated receptor gamma (PPAR-γ) nuclear transcription factor and are effective drugs to achieve glycaemic control in patients with type 2 diabetes mellitus. Recent rapidly growing evidence suggests that glitazone use is associated with accelerated bone loss and an increased risk of fracture. This review aims to evaluate the current knowledge of adverse effects of glitazone therapy on the skeleton. Articles in English, Spanish, German and French published up until April 2009 are included. Results from preclinical studies have demonstrated that activation of PPAR-γ inhibits bone formation by primarily diverting mesenchymal stem cells to the adipocytic rather than to the osteogenic lineage, and that glitazones may increase bone resorption by stimulating osteoclasts. Numerous studies in humans have demonstrated decreased bone turnover, accelerated bone loss and impaired bone mineral density both in healthy volunteers and in patients with type 2 diabetes. Furthermore, results from recent large, randomized controlled trials and from observational studies provided evidence for an increased fracture risk for glitazone users, mostly for women, but possibly also for men. As a consequence of these observations, clinicians should carefully assess the fracture risk in patients with type 2 diabetes before starting therapy with glitazones.

The insulin-sensitizing thiazolidinediones (commonly known as glitazones) are an important class of oral antidiabetic agents. Pioglitazone and rosiglitazone account for more than 20% of the oral antidiabetic drugs prescribed in the US and for approximately 5% in Europe.[1] In addition to their established role in the treatment of patients with type 2 diabetes mellitus and impaired glucose tolerance,[2] glitazones have been used in the pharmacotherapy of polycystic ovary syndrome (POCS).[3] POCS is associated with insulin resistance, and affected women are at increased risk for type 2 diabetes.[4] Recently, rosiglitazone has been shown to improve elevated transaminase levels and liver steatosis in patients with non-alcoholic steatohepatitis, a condition strongly associated with type 2 diabetes and characterized by hepatic insulin resistance.[5] However, the role of glitazones in the treatment of non-alcoholic steatohepatitis still remains to be established.

Rosiglitazone and pioglitazone are agonists of the peroxisome proliferator-activated receptor (PPAR)-γ nuclear transcription factor.[6] Pioglitazone, in contrast to rosiglitazone, also exhibits PPAR-α agonist activity, which may help to explain why pioglitazone has more favourable effects on plasma lipids than rosiglitazone.[7,8] Rosiglitazone has been shown to improve glycaemic control in patients with type 2 diabetes in comparison with either metformin or glibenclamide (glyburide),[9] and to improve glycaemic control in sulphonylurea-treated patients when added early on to a glimepiride therapy.[10] Glitazones are generally well tolerated. Weight gain, oedema, anaemia and extracellular volume expansion due to fluid retention have been observed; oedema has been reported in 4–6% of patients undergoing treatment with glitazones compared with 1–2% of those receiving other oral hypoglycaemic agents or placebo.[6] Recent evidence suggests that rosiglitazone may increase the risk of cardiovascular events such as heart failure and myocardial infarction.[11-15] In comparison with rosiglitazone, pioglitazone may exhibit favourable effects on cardiovascular events and risk factors.[16-20] Recent, rapidly growing evidence further suggests that glitazone use is associated with accelerated bone loss and an increased risk of fracture, especially in the distal upper limb (forearm, wrist, hand) or distal lower limb (foot, ankle, fibula and tibia).[21,22] This review aims to evaluate the current knowledge of adverse effects of glitazone therapy on the skeleton. Articles published in English, Spanish, German and French until April 2009 were retrieved via searches of Medline, ClinicalTrials.gov, bibliographies and conference abstracts. Articles were eligible for our analysis if they reported results from randomized controlled trials, reviews, meta-analyses, case-control studies, cohort studies, or case series. Articles were identified using the following search terms: 'thiazolidinediones', 'glitazones', 'rosiglitazone', 'pioglitazone', and/or 'bone', 'fracture', 'bone mineral density', 'bone loss'.

1. How do Glitazones Affect Bone Metabolism?

Glitazones act as agonists of PPAR-γ, which regulates many processes, including insulin action, adipocyte differentiation, lipid metabolism, inflammation, atherosclerosis, kidney function and cancer. There is a substantial body of evidence from *in vitro* studies that PPAR-γ is expressed in bone marrow stroma cells, osteoblasts and osteoclast precursors.[23,24] Activation of PPAR-γ in bone marrow stroma cells by high doses of rosiglitazone promotes adipogenesis with predominant formation of adipocytes from mesenchymal pluripotent stem cells while suppressing development of osteoblasts.[25] In accordance with these findings, in cultures of bone marrow stroma cells derived from PPAR-γ-deficient mice, more osteoblasts are formed compared with cell cultures from wild-type mice.[26] Taken together, activation of PPAR-γ *in vitro* is associated with preferential formation of adipocytes and suppressed development of osteoblastic cells.[27]

Studies investigating PPAR-γ signalling on osteoclast development and/or osteoclastic function yielded conflicting results. In both murine bone marrow cells[28] and in a co-culture of human mesenchymal and hematopoietic stem cells,[29]

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glitazone-associated PPAR-γ agonist activity inhibited the formation of osteoclasts. This effect was mainly attributed to a direct effect on osteoclastic precursors. These results were supported by evidence of impaired osteoclastogenesis from human mononuclear cells as osteoclastic precursors.[30] In contrast to these findings, however, development, function and life span of osteoclasts were not affected in PPAR-γ-haploinsufficient mice.[26]

In recent years, various animal studies have confirmed adverse skeletal effects of glitazones.[23,24,31] The most consistent findings of these studies were decreased bone formation and diminished bone mass. Most probably, these effects are attributable to the diversion of pluripotent mesenchymal stem cells from the osteoblastic to the adipocytic lineage. In accordance with this explanation, in most reports bone marrow adiposity increased.[32]

Whether glitazones affect bone resorption is less clear. Several studies reported increased bone resorption in rodents treated with glitazones, while other reports could not confirm these findings.[31] Interestingly, administering rosiglitazone to older rodents promoted osteoclast differentiation and decreased bone mass.[33-35]

A transgenic mouse model lacking one copy of the PPAR-γ gene exhibited increased bone mass with increased bone formation and decreased adipogenesis. However, bone resorption was not affected.[36] Another study using a mouse model with deletion of the 12/15-lipoxygenase gene, resulting in diminished synthesis of naturally occurring PPAR-γ agonists, reported increased bone mass.[37] Specifically deleting the PPAR-γ gene in mice osteoclasts resulted in osteopetrosis due to impaired osteoclastogenesis.[34]

In conclusion, the results from *in vitro* and animal studies provide evidence that activation of PPAR-γ signalling is strongly associated with decreased bone mass, which occurs largely because of inhibited osteoblast differentiation and function. However, as indicated above, activated bone resorption in older rodents may be an important co-factor contributing to the observed decrease in bone mass.

2. Do Glitazones Exhibit Adverse Skeletal Effects in Humans?

Current evidence suggests that rosiglitazone and pioglitazone exert adverse effects on skeletal health such as accelerated bone loss, decreased bone mineral density and increased risk for fractures. In the Health ABC (Aging, and Body Composition) study, a prospective cohort study of Americans aged 70–79 years, use of glitazones was associated with accelerated bone loss in the whole body, femoral neck and lumbar spine in diabetic women. In contrast, no effect of glitazones on bone mass could be observed in 32 male subjects.[38] Glintborg et al.[39] observed decreased bone mineral density at the femoral neck and in the lumbar spine in 30 patients with POCS treated with pioglitazone for 16 weeks, compared with placebo.

In addition to the measurement of bone mineral density, the assessment of biochemical markers of bone turnover may further reflect effects of glitazones on bone-forming osteoblasts and bone-resorbing osteoclasts. Serum alkaline phosphatase and parathormon levels decreased significantly in patients treated with pioglitazone.[39] In a study by Okazaki et al.,[40] administration of troglitazone to 33 patients with type 2 diabetes for 4 weeks reduced bone turnover with a decrease in markers of bone formation and bone resorption. Berberoglu et al.[41] reported significantly lower bone-specific alkaline phosphatase levels, indicating decreased bone formation, 12 weeks after initiation of rosiglitazone treatment in 28 obese, postmenopausal, diabetic women. There were no statistically significant changes in osteocalcin or deoxypyridinoline serum levels in the rosiglitazone group compared with diet alone.

In healthy postmenopausal women, short-term treatment with rosiglitazone over 12 weeks resulted in decreased bone formation markers, such as procollagen type I N-terminal propeptide and osteocalcin. These changes became evident as soon as 4 weeks after initiation of rosiglitazone administration and persisted for the whole observational period. In addition, a significantly decreased hip bone mineral density was observed in the rosiglitazone group compared with the

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placebo group. In contrast to the altered levels of markers of bone formation, there was no change in the serum β-C-terminal telopeptide (β-CTX), a marker of bone resorption.[42]

In our own recent nested case-control analysis, we observed an increased relative risk of fractures (predominantly at wrist and hip) in users of glitazones compared with non-use of this drug class in patients with type 2 diabetes. After 12–18 months of therapy, adjusted odds ratios (ORs) in users of rosiglitazone or pioglitazone, compared with non-use of the respective drug class, were 2.43 (95% CI 1.49, 3.95) and 2.59 (95% CI 0.96, 7.01), respectively.[43] Of note, these findings were adjusted for age, sex, geography, calendar time, concomitant oral antidiabetic drugs, comorbidities, smoking status and body mass index, and they tended to increase with cumulative glitazone dose. Remarkably, we found an increased risk of fractures not only in women but also in men, providing evidence that glitazones may exert clinically important detrimental effects on the male skeleton, also. In addition, more than 60% of our study population was above 70 years of age, the population at highest risk for bone fractures due to osteoporosis. In our data analysis, based on computerized primary-care data from the UK (General Practice Research Database, GPRD), we certainly missed some cases with vertebral fractures since systematic radiographic screening for the identification of asymptomatic vertebral deformities and fractures was not available. To assess not only symptomatic but also asymptomatic vertebral fractures, radiographic studies would have been needed before and after exposure to the drug of interest in each patient. Importantly, adjustment for duration of diabetes and use of insulin left the results unchanged. In accordance with our findings, Yaturu et al.[44] reported a highly significant, up to 6-fold increase, in the rate of bone loss in diabetic male patients treated with rosiglitazone for an average of 16 months, both at spine and proximal femur.

In ADOPT (A Diabetes Outcome Progression Trial), a large, randomized, double-blind study, the investigators compared the durability of the treatment effect of rosiglitazone, metformin or glibenclamide on glycaemic control over 4 years in 4360 patients aged 30–75 years with recently diagnosed type 2 diabetes. Within this cohort a significantly increased risk of fractures in female (but not in male) patients with type 2 diabetes using rosiglitazone has been reported. In 60 female patients (9.3% of all patients), predominantly upper and lower limb fractures were reported in users of rosiglitazone in comparison with 30 (5.1%) fractures in metformin and 21 (3.5%) in glibenclamide users. The calculated cumulative incidence of fractures in women at 5 years was 15.1% for rosiglitazone, 7.3% for metformin and 7.7% for glibenclamide users. The increase in fracture rates with rosiglitazone occurred in both premenopausal and postmenopausal women. In addition, no particular risk factor for fracture was identified in the female patients receiving rosiglitazone therapy.[9,45]

In PERISCOPE (Pioglitazone Effect on Regression of Intravascular Sonographic Coronary Obstruction Prospective Evaluation), a randomized, controlled trial investigating the impact of pioglitazone and glimepiride on the progression of coronary atherosclerosis, 8 of 270 (3%) patients in the pioglitazone group and none of 273 in the glimepiride group developed a bone fracture ($p = 0.04$). However, it was not reported whether or not only female patients were affected.[18] It is important to note that in these two trials there was no placebo comparator. However, the available evidence suggests that other oral hypoglycaemic agents do not alter the fracture risk.[15,43]

Takeda, the manufacturer of pioglitazone, reported findings from an analysis of their clinical trial database, comparing more than 8100 patients treated with pioglitazone with more than 7400 patients receiving either placebo or an oral hypoglycaemic agent from a different class. In this study, the incidence of fractures was 1.9 per 100 patient-years in the pioglitazone group and 1.1 per 100 patient-years in the comparator group. This translates into an excess risk of fracture in the patients treated with pioglitazone to 0.8 fractures per 100 patient-years of use[21] and resulted in a US FDA warning in 2007.[46] Soon after the first alert, the FDA posted a

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warning in February 2008 for rosiglitazone after GlaxoSmithKline discovered adverse skeletal effects in their clinical trial database.[22] Recently, Loke et al.[47] analysed 13 715 patients from ten randomized, controlled trials and found an increased risk of fractures for women (OR 1.45 [95% CI 1.65, 3.01]) but not in men (OR 1.00 [95% CI 0.73, 1.39]).

Taken together, these results provide growing evidence that possibly even short-term use of glitazones in clinically relevant doses is associated with adverse skeletal effects, and that these effects are associated with an increased risk of fractures. In most studies, women were affected, but there is evidence that men may also be at risk.[43,44]

From a mechanistic point of view, in concordance with most *in vitro* experiments and animal studies, decreased bone formation may be the most important contributor to the observed bone loss in humans and to the elevated fracture risk in association with use of glitazones. However, one cannot exclude the possibility that an inadequately elevated rate of bone resorption may play a role as 'normal bone resorption' in association with decreased bone formation may be inappropriate considering the tight coupling of formation and resorption of bone tissue.[23]

Most authors reported upper and lower limb fractures, namely of wrist, humerus, hip and fibula. Taking into account that most of the trials involving glitazones were not designed to detect adverse skeletal events, data about adverse effects on the skeleton were not collected systematically in a prespecified manner. As a consequence, evaluation of vertebral fractures was not possible, and under-reporting might have occurred. Of importance, most studies were conducted in relatively young patients with a mean age of about 60 years who therefore were at a rather low risk for fracture. Thus, it is not surprising that the classical pattern of osteoporotic fracture was not observed. In accordance with this observation, epidemiological studies in non-diabetic populations of the same age reported similar patterns of fractures, predominantly affecting the limbs.[48,49]

As mentioned earlier, the use of glitazones in animals causes an increase in bone marrow adiposity.[25] Currently, we do not know whether the same phenomenon occurs in humans as well. Nevertheless, there is growing evidence that a reciprocal relationship between marrow adiposity and bone formation may exist in humans, although it is not clear whether there is a causal relationship.[23,32]

3. Type 2 Diabetes Mellitus and the Risk of Fracture

Epidemiological studies suggested that type 2 diabetes is an independent risk factor for adverse effects on the skeleton. Nicodemus and Folsom[50] reported a higher relative risk (adjusted OR 1.7 [95% CI 1.21, 2.38]) of incident hip fractures in postmenopausal women who developed type 2 diabetes, compared with non-diabetic postmenopausal women. Longer duration of type 2 diabetes was associated with a higher fracture risk, as was use of insulin or oral hypoglycaemic medications in women with type 2 diabetes. Schwartz et al.[51] also reported an increased risk of hip, foot and proximal humerus fracture in type 2 diabetic female patients. Recently, more studies added substantial evidence that type 2 diabetes itself is an independent risk factor for fractures.[52-56]

The question arises how type 2 diabetes can increase skeletal fragility. It is evident that low bone mass cannot be responsible since axial bone mineral density is even higher in type 2 diabetic patients than in non-diabetic patients.[23,51,52,54] However, bone in diabetic patients may be more fragile for a given bone mineral density.[57] A decreased bone mass has been associated with an increased risk of fractures in diabetic patients compared with diabetic patients with normal bone mineral density.[53] In addition, diabetic complications such as neuropathy, retinopathy, stroke or myocardial infarction increase the risk of falls[58,59] and consequently the risk of fracture. It has also been discussed whether neuropathy itself may reduce bone mass.[60] There is also evidence that older White diabetic women lose bone at the hip more rapidly than those without diabetes.[61]

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4. Clinical Considerations and Implications

While it appears well established that glitazones exert detrimental effects on the human skeleton, several questions remain to be answered. First, we currently do not know the magnitude or the possible reversibility of bone loss in humans associated with long-term use of glitazones. Second, the effects of glitazone use on the male skeleton are not fully understood. Only a few studies suggest that males are also affected, while most of the current knowledge results from evidence of fractures and bone loss in women. Third, there is currently no evidence-based information available addressing possible therapy or prevention measures of glitazone-induced bone loss.

Considering that both type 2 diabetes and the use of glitazones seem to be independently associated with an increased risk of adverse skeletal effects, including an increased risk of fracture (at least in women), clinicians must carefully weigh up risk and benefits for individual patients before selecting rosiglitazone or pioglitazone as an oral hypoglycaemic agent. Recent guidelines for treating type 2 diabetes do not advocate use of glitazones as first-line treatment but, among other options, can be considered as a third-line treatment option in patients with poor glycaemic control.[62-64] Glitazones effectively decrease glycosylated haemoglobin (HbA_{1c}) in patients with type 2 diabetes, but they also have been associated with adverse cardiovascular effects, weight gain, oedema and anaemia as consequences of expanded extracellular volume. In addition, as demonstrated here and discussed recently in the literature,[23,31] glitazone use in diabetic patients has been associated with adverse skeletal effects.

Type 2 diabetes itself is strongly associated with cardiovascular morbidity and mortality from both micro- and macrovascular disease. In addition, risk of fracture and accelerated bone loss is an important issue in diabetic patients. Therefore, selecting a class of oral hypoglycaemic agents with clinically relevant adverse effects on bone and cardiovascular system seems problematic and cannot be advocated without restriction. When considering glitazones for patients with type 2 diabetes, physicians must be aware that postmenopausal women treated with these medications are at increased risk of fractures. Before starting glitazone therapy it is advisable to assess clinical skeletal risk factors such as female sex, age, postmenopausal state, bodyweight, fracture history and smoking history.[23] It has to be kept in mind that measurement of bone mineral density by dual energy x-ray absorptiometry (DEXA) may not be helpful in identifying diabetic patients at highest risk for fractures as, in most patients with type 2 diabetes, bone mineral density is increased compared with non-diabetic controls. Specifically, whereas low bone mineral density is associated with an increased risk of fracture in patients with type 2 diabetes, normal bone density results do not exclude increased fracture risk in these patients. At present, the best strategy may be to avoid use of glitazones in patients at high risk of fracture.

For patients for whom glitazone treatment is desirable, administration of adequate calcium and vitamin D supplementation and advising adequate exercise might help to minimize the skeletal impact of glitazones. While this is a rather general recommendation, it has to be emphasized that there is currently no data available providing evidence for an altered risk of fractures in association with use of calcium and vitamin D supplementation or with regular exercise for patients using glitazones. From a pathophysiological perspective, an anabolic drug, such as teriparatide, would be the most likely agent to improve bone density and decrease fracture risk. However, as shown for patients with glucocorticoid-induced bone loss, antiresorptive agents (such as bisphosphonates) may also be effective. It could therefore be speculated that bisphosphonates may attenuate the adverse skeletal effects of glitazones, as they do in treatment of glucocorticoid-induced osteoporosis.[65] It must be emphasized again though, that currently there are no data supporting such possible effects of antiosteoporotic treatment on glitazone-induced bone loss.

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5. Conclusion

Recent evidence suggests that glitazone use is associated with accelerated bone loss and an increased risk of fracture in humans. Preclinical studies have demonstrated that activation of PPAR-γ by glitazones inhibits bone formation. Numerous studies in humans have demonstrated decreased bone turnover, accelerated bone loss and impaired bone mineral density both in healthy volunteers and in patients with type 2 diabetes. In addition, results from clinical trials and observational studies provide substantial evidence for an increased fracture risk for glitazone users, mostly for women, but possibly also for men. As a consequence of these observations, clinicians should carefully assess the fracture risk in patients with type 2 diabetes before starting therapy with glitazones.

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