Thiazolidinediones and bone

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Summary

Diabetes mellitus and osteoporosis are two frequent multifactorial medical conditions with an increasing prevalence in the aging population. Patients with type 2 diabetes mellitus have an increased fracture risk despite a higher bone mineral density (BMD), which is mainly due to the increased risk of falls. Adequate glycemic control and prevention of diabetic complications are also the mainstay of therapy in type 2 diabetes mellitus. The thiazolidinediones (TZDs) have been demonstrated to improve insulin sensitivity and currently represent a widely prescribed treatment for type 2 diabetes. Their action is mediated by the binding to the nuclear receptor and transcription factor, peroxisome proliferator-activated receptor-γ (PPAR-γ), regulating the activity of other transcription factors in the adipogenic differentiation and inflammatory response pathways. The activation of PPAR-γ by TZDs may also cause an increase in bone marrow adiposity and a decrease in osteoblastogenesis, resulting in reduced bone formation. Clinical data are pointing out that the intake of thiazolidinediones by older patients with type 2 diabetes correlates with both the decrease of bone mineral density in the femoral neck and hip and a higher risk for fractures. Thus, health care providers, not only physicians, should carefully check the existence of risk factors for osteoporosis and factures in their patients before selecting them for thiazolidinediones treatment. Moreover, an adequate clinical follow-up of treated subjects is strongly recommended.

KEY WORDS: thiazolidinediones, metabolic bone disorders, fracture risk.

Introduction

Type 2 Diabetes Mellitus (T2DM) is characterized by peripheral insulin resistance with a variable degree of hyperinsulinemia and impaired insulin secretion following metabolic challenge by glucose. Long standing hyperglycemia leads to non-enzymatic glycosylation of various bone proteins, including type I collagen, which may impair the bone quality. Other skeletal effects of hyperglycemia are represented by glycosuria-related hypercalciuria and perturbation of the PTH (parathyroid hormone)/vitamin D axis.

In 1980, a large retrospective study described that diabetes was not associated with increased risk of fracture except at the ankle level (1). In T2DM females, Bonds et al. reported an overall risk of fracture higher in subjects with diabetes at baseline, also considering their higher frequency of falls (2). In fact, a recent review reported that women with T2DM, despite a higher bone mineral density (BMD), display a 1.7-fold increased hip fracture risk, which is mainly attributable to the increased risk of falling, as also previously assessed by the Rotterdam Study (3).

Interestingly, the adverse effects of hyperglycemia on the skeleton are largely counteracted by the positive effects of obesity on BMD. In fact, it has been suggested that obesity may protect against bone loss according to the findings that BMD and body mass index (BMI) are positively correlated in patients with T2DM (4, 5) and that the BMI in these patients negatively associates with the presence of osteoporosis (6).

Moreover, it has been reported that axial BMD negatively correlates with the duration of T2DM (7), whereas cortical BMD negatively associates with mean hemoglobin A1c (HbA1c) serum levels, an index of poor metabolic control (7).

Adipose tissue produces peculiar cytokines, namely adipokines, such as leptin, resistin, and adiponectin, that may modulate the BMD increases. Recently, an inverse association between adiponectin serum levels and BMD, at different skeletal sites, has been reported in patients with T2DM (8).

Thiazolidinediones (TZDs) are ligands for peroxisome proliferator activated receptor-γ (PPAR-γ), a family of nuclear receptors able to regulate gene transcription. PPAR-γs expression is particularly abundant in adipocytes in which they regulate differentiation and function. A lower expression of PPAR-γs has been reported in pancreatic islet cells, liver, skeletal muscle, vascular endothelium, and bone.

TZDs have been considered an elective treatment for diabetes increasing insulin sensitivity through activation of PPAR-γ pathway. It is known that activation of PPAR-γ improves glucose metabolism by enhancing tissue sensitivity to insulin, primarily through its action on adipose cells.

However, early studies suggested that TZDs were no more effective in lowering glycemia than older oral medications (9). These findings, the previously reported side effects of the TZDs (such as weight gain, fluid retention, and the risk of congestive heart failure) and the higher cost of brand-name TZDs than that of generic metformin, determined a reconsideration of their line positioning in the choice of treatment of diabetes (10).

Rosiglitazone and pioglitazone are currently the commercially available TZDs for therapeutical purposes. It has been reported that during 2005, in the USA, they have been prescribed over 22 million times (http://www.diabetesdaily.com/forum/research-clinical-trials/3480-tzds-broken-bones). Both drugs have been shown to reduce either glycemia or HbA1c through an increase sensitivity to insulin through the lowering of insulin resistance. However, considering the relationships between glycemic ben-

efit of rosiglitazone, its related risk of fluid retention and weight gain, and its higher cost, also due to the need for more statins and diuretics, metformin could be still considered the preferred first choice in the pharmacotherapy for T2DM (11).

Major pitfalls in the clinical use of TZDs: not only hepatotoxicity

Several adverse effects of TZDs have been emerging from the postmarket analyses. In 2000, Parke-Davis/Warner Lambert agreed to the FDA's request to withdraw its TZD, called troglitazone (Rezulin), from the market because of severe hepatotoxicity (http://www.fda.gov/bbs/topics/news/new00721.html). In fact, troglitazone was found to be more toxic to the liver than rosiglitazone and pioglitazone.
TZDs have been also implicated in causing edema (12).

TZDs: are they osteotoxic?

In vitro and animal studies

Effects on osteoblasts

It has been reported that activation of PPAR-γ by TZDs may cause an increase in bone marrow adiposity and a decrease in osteoblastogenesis, resulting in reduced bone formation (13). TZDs may exert their effects on enhanced insulin sensitivity through the regulation of adiponectin secretion by fat cells (14). Indeed, receptors for adiponectin have been demonstrated in bone, and *in vitro* studies suggested that adiponectin is able to stimulate osteoblast differentiation (15, 16). Although the exact mechanism is still unclear, it is thought that its agonistic activity to PPAR-γ may promote the differentiation of precursor cells into adipocytes instead of transforming them into osteoblasts, influencing also the lineage allocation of mesenchymal stem cells (MSC) in the bone marrow. Indeed rosiglitazone exhibits all these actions.
As a consequence, TZDs are reported to cause bone loss in some rodent models (13, 17-19), but not in all (19). Interestingly, in mice the haploinsufficiency of the PPAR-γ gene induces a high bone density phenotype with an increased rate of osteoblastic bone formation (20, 21), whereas a deficient osteoblast function and a consequent bone loss have been reported in rodents treated with PPAR-γ agonists (13, 20, 21). In animal models, this observation was particularly true in ovarectomized rats, but not in male animals (http://www.diabetesdaily.com/forum/research-clinical-trials/3480-tzds-broken-ones).
Overall, in the rodent models, rosiglitazone treatment decreases osteoblast function and increases bone loss (13, 17, 22). In addition to bone loss, in the animal models rosiglitazone treatment results in greater marrow adiposity (13, 22).

Effects on osteoclasts

The effect of PPAR-γ activation on osteoclasts has not been clearly established. Some animal models did not exhibit a different resorption function (13, 17, 22), but others were found to show an increased bone resorption (18). Through a co-culture system approach, Okazaki et al. (23) and Mbalaviele et al. (24) demonstrated that specific PPAR-γ agonists, including the not commercially available compound ciglitazone, cause a dose-dependent blockage of osteoclast formation and resorption.
Recently, activation of individual PPARs with isoform-specific agonist resulted in significant dose-dependent inhibition of multinucleated osteoclast formation. In particular, ciglitazone and L165041 compounds resulted respectively to inhibit and to stimulate osteoclastic function. Thus, isoform-specific PPAR agonists may play strong effects on multinucleation with variable effects on bone resorption (25).
Although the exact mechanism behind this inhibition of osteoclast formation and resorption has not yet been determined, it is known that PPAR-γ is able to antagonize the transcription factor NF-κB (26) which is the fundamental pathway for RANKL signaling and essential for osteoclast development, survival and function (27).
No data are currently available on a possible role of TZDs on osteocytes.

Clinical findings in humans

TZDs and risk for bone fractures

Little information is available on the effects of TZDs on bone in humans. The increased use of TZD treatment and the recognized evidence that T2DM is associated with a higher risk of fracture, represented important bases for investigation on the possibility that TZDs can cause bone loss in humans. If this was true, one should rethink their therapeutical use, at least in patients with an increased fracture risk. Unfortunately, due to the fact that the use of TZDs in T2DM is relatively recent, only few reports on TZD therapy and fracture risk are currently available.
Interestingly, Asian women with a *PPARγ* polymorphism exhibit a reduced bone mineral density (28) and lower circulating osteoprotegerin levels (29), suggesting a direct role of PPAR-γs in bone metabolism. It has been suggested that the TZDs might decrease bone turnover independently of their effects on glucose metabolism, through a decreased bone-resorption, evaluated by bone turnover markers assessment, in T2DM patients. More definite findings are needed by independent studies as also whether this effect will consists of an increase in bone mineral density and a decrease in fracture risk in T2DM patients.
In the study by Okazaki et al., on T2DM patients, it has been also found that a 4 weeks troglitazone treatment reduced markers of bone turnover by 7-18% (23). Later, a small study on troglitazone use reported that the bone mineral density Z-scores at the lumbar spine was not changed after 12 months of treatment in 25 diabetic patients. Moreover, bone turnover markers levels, such as urinary type 1 collagen, N-telopeptide and serum bone alkaline phosphatase, resulted reduced after the first month of treatment, returning to baseline levels by 12 months (30).
On the contrary, more recent studies have reported that T2DM individuals exhibited a higher risk for hip (31-38), proximal humerus (33, 34), foot (33, 38), and all nonvertebral fractures combined (33, 34, 36, 39).

Bone fractures in patients treated with TZDs involve "non classical" skeletal sites?

In a randomized, double blind parallel group study, named "A Diabetes Outcome Progression Trial (ADOPT)", the bone-related adverse events associated with this drug use were described (40). The trial, that compared glycemic control in patients taking rosiglitazone, metformin, or glyburide, involved 4360 patients aged 30 to 75 years with recently diagnosed T2DM who were followed for 4 to 6 years. Only 30 subjects had fractures in the metformin and 20 in the glyburide group, with 60 patients fracturing in the rosiglitazone group. Fracture risk was the same across groups in men, with higher incidence in women taking rosiglitazone.
Fracture sites were considered "atypical" for postmenopausal osteoporosis, that normally involves the spine and the hip, with women in the rosiglitazone arm experiencing prevalent fractures of the upper arm, hand, or foot when compared to the other treatment arms.

Data from the Nurses' Health Study (41) suggests a 6-fold higher risk of hip fracture in patients with type 1 diabetes mellitus and twice the risk in patients with T2DM. Other studies demonstrated an increased risk of fractures of the hip, humerus and foot in diabetic patients treated with insulin, with no increase in vertebral fractures. Patients with diabetes are also at higher risk for falls than non-diabetic patients (41).
In addition, recent clinical observations from the Health ABC trial indicated a 2.5-fold accelerated bone loss in postmenopausal diabetic women using TZDs, but not in men (22 patients taking troglitazone, 30 pioglitazone and 31 rosiglitazone), with an additional annual bone loss in older diabetic women using any TZD lower (0.5% at the total hip and 1.2% at the spine) (42).
A recent randomized clinical trial from New Zealand demonstrated that 8 mg of rosiglitazone daily decreases bone mass and bone formation in 50 postmenopausal women without diabetes (43). The trial enrolled healthy postmenopausal women who did not have diabetes or osteoporosis and after 14 wk of treatment with rosiglitazone, the subjects experienced a significant decrease in bone density (-1.9% rosiglitazone vs. -0.2% placebo) at the total hip accompanied by a modest reduction (-8 to -13%) in bone formation markers without a change in resorption markers. No data are available on the possibility that bone loss continues or bone density stabilizes or even recovers (43). In an Editorial to this paper Schwartz and Sellmeyer reported: "If the rate of bone loss identified in this trial (43) continued for a year, the additional loss with rosiglitazone therapy would be 6.8%, compared with an average loss in postmenopausal women of about 1% annually" (44). A criticism that can be moved to this trial is represented by both the short duration and the fact that a healthy population was evaluated. Conversely, the latter issue can also represent an advantage, allowing the assessment of rosiglitazone side effects on bone metabolism, independently on any other confounding factor (43).
Thus, these findings by Grey et al., clearly established the evidence for a detrimental effect of PPAR-γ agonists on the postmenopausal female skeleton (43). A randomized controlled trial also in men will be necessary in order to define a gender difference in the skeletal response to TZDs.

Warnings from Pharmaceutical Companies and Institutions

The use of rosiglitazone and pioglitazone clearly showed "dangerous effects" in some patients. Therefore, both the FDA and Takeda Pharmaceuticals North America Inc, the manufacturer of pioglitazone, notified health care professionals that clinical trial data indicated that the female patients treated groups pioglitazone exhibited more fractures than comparators (either placebo or other drugs).
Takeda's letter to clinicians noted that the fracture incidence was 1.9 fractures per 100 patient-years in the pioglitazone treated group compared with 1.1 fractures in the comparator-treated groups (http://www.fda.gov/medwatch/safety/2007/safety07.htm#Glycerin).
This translates in an excess risk of 0.8 fractures per 100 patient-years of use for women taking the drug. Further evaluation of these findings is ongoing and the Company stated that "none of the pioglitazone studies addressed, or were designed to study, the effect on bone, but fractures were collected as adverse events".
The warning was sent out on 3/9/07 for pioglitazone, as increased risk for fractures in the distal arms and legs was observed in postmenopausal women.
The numbers and the unexpected fracture sites reported by Takeda correspond well with observations for rosiglitazone. The FDA posted a similar warning in February for the drug rosiglitazone (http://www.fda.gov/medwatch/safety/2007/safety07.htm#rosiglitazone). At the manufacturer's request, an independent Safety Committee reviewed fractures in another large, ongoing, controlled trial, and a preliminary analysis was consistent with the observations from ADOPT.

Open questions

Common sense suggests the need to identify and minimize risk factors for falls (advanced age, impaired balance, cardiovascular disease, neuropathy) in subjects with reduced BMD through implementation of a program combining regular exercise, adequate vitamin D supplementation, withdrawal of psychotropic medications when possible, visual assessment, environmental hazard assessment and modification, and the use of hip protectors. Although more basic and clinical research data will be necessary to elucidate the relationship among TZDs therapy, bone metabolism and risk fractures, some practical indications are emerging.

What does this could represent in the daily clinical practice of health care providers?

It is mandatory to advice health care providers on the possibility of increased bone loss and fracture risk associated with TZDs use. In fact, current data strongly suggest a higher risk for adverse skeletal effects in middle-aged and older women. An overall survey considering all the existing fractures risk in the population of subjects to be treated has to anticipate the choice of treatment.
Consequently, an accurate evaluation of the pre-existing patient's fracture risk needs to be adequately performed in each subject before prescribing TZD therapy. Adequate osteoporosis therapy should be initiated in those women exhibiting a reduced bone density and other risk factors for fracture at the baseline. Additional studies are needed to ascertain the degree of bone loss and fracture risk in postmenopausal women associated with long-term TZD therapy and to identify whether TZDs have negative skeletal effects in men and premenopausal women.
It is obvious that all T2DM patients at risk should optimize nutrition and lifestyle factors in any case to better protect skeletal health, independently by the decision for a treatment with TZDs.

How to correctly select patients you would not start on TZDs and how to correctly recognize patients you would even take off these drugs?

All the patients to be eventually treated by TZDs are strongly recommended to undergo careful evaluation of both bone mass and bone turnover markers at the beginning and periodically during therapy, in order to reduce the occurrence of fractures, worsening the quality of life, and consequently their related socio-economical costs.
An accurate osteoporosis screening is strongly suggested also for T2DM older men at baseline, evaluating possible causes of secondary osteoporosis, such as pre-existing medical status or drugs capable to induce bone loss.
However, since rosiglitazone may increase marrow fat, it has to be considered that the extent and the rate of bone loss during therapy may not be accurately assessed using the gold standard dual energy x-ray absorptiometry (DXA). Indeed, DXA scans may suffer because of the artificial decreases in bone

mineral density (BMD) associated to an increased marrow fat (19, 45).
Of course, it should be recommended that physicians, who potentially have to face such problems, must be adequately and appropriately informed on both the correct management of bone disorders and the correct interpretations of the new warnings occurring in this field.

Do these findings on bone fractures limit the potential beneficial effects on glycemic control by TZDs?

Given the known benefits of TZD therapy for diabetes, the benefits of therapy may still outweigh the side effects, particularly in those with a low risk of fracture.
According to these findings it is clearly emerging the need of keeping a close control on the TZDs' potential dangers for both study participants and diabetic patients in the general population.

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