Thiazolidinediones and Their Effect on Bone Metabolism: A Review

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ABSTRACT

Thiazolidinediones (TZDs) are a class of antihyperglycemic agents commonly used in the treatment of type 2 diabetes mellitus. It is accepted that through activation of peroxisome proliferator-activated receptor (PPAR) gamma, TZDs have an effect on bone metabolism. People with diabetes are already at an increased risk of fractures due to multiple factors, but recent incidental findings in A Diabetes Outcome Progression Trial (ADOPT) have introduced the idea that TZD use may increase fracture risk in women. This review article will summarize the current evidence regarding the effect of TZDs on bone metabolism in vitro and in animal and human studies, with an emphasis on their effects on bone mineral density and changes in bone turnover markers. The available but limited evidence investigating the relationship between TZD use and fracture risk will also be addressed.

KEYWORDS

Fractures, osteoporosis, thiazolidinediones

RÉSUMÉ

Les thiazolidinédiones (TZD) sont une classe d'antihyperglycémiants administrés couramment pour le traitement du diabète sucré de type 2. Il est reconnu qu'en activant les récepteurs PPAR-gamma, les TZD ont un effet sur le métabolisme osseux. Chez les personnes atteintes de diabète, il y a déjà un risque accru de fractures en raison de multiples facteurs, mais de récentes données provenant de l'essai ADOPT (*A Diabetes Outcome Progression Trial*) semblent indiquer que les TZD pourraient accroître le risque de fractures chez les femmes. Cet exposé de synthèse résume les données actuelles sur l'effet des TZD sur le métabolisme osseux observé *in vitro* et au cours des études menées chez les animaux et les humains, et met l'accent sur leurs effets sur la densité minérale osseuse et les marqueurs du renouvellement osseux. Dans cet exposé, il est également question des données disponibles mais limitées sur le lien entre les TZD et le risque de fractures.

MOTS CLÉS

Fractures, ostéoporose, thiazolidinédiones

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INTRODUCTION

Thiazolidinediones (TZDs) are a group of commonly prescribed and effective oral glucose-lowering medications used in the treatment of type 2 diabetes. Pioglitazone and rosiglitazone are the TZDs currently approved for clinical use; they are generally well tolerated and complement other antihyperglycemic therapies (1). There is evidence that the use of TZDs may increase the risk of fractures, but currently no trial has been designed to directly investigate the relationship between TZD use and an increase in the frequency of fractures, although recent studies have used changes in bone mineral density (BMD) and markers of bone turnover to indirectly assess fracture risk. This review will present some of the current evidence regarding TZDs and changes in bone metabolism in both human and animal studies; the limited evidence investigating the relationship between TZD use and fracture risk will also be addressed.

MECHANISM OF ACTION

TZDs reduce plasma glucose levels by increasing insulin sensitivity in muscle, adipose tissue and the liver, and because of this action, they have become a useful agent in the treatment of type 2 diabetes (2). There is also evidence that the use of TZDs in patients with impaired fasting glucose, or impaired glucose tolerance (IGT) may preserve pancreatic beta-cell function, thereby delaying and/or preventing the onset of type 2 diabetes in this high-risk population (3). TZDs exert their action through the activation of a peroxisome proliferator-activated receptor (PPAR)-gamma family of nuclear transcription factors. The PPAR-gamma receptor can bind to a number of ligands, including TZDs, polyunsaturated fatty acids and oxidized metabolites of prostaglandin J2 (4). In response to ligand binding, PPAR-gamma dimerizes with another nuclear receptor, the ligand-bound retinoid X receptor, to form an active transcription factor (5). This heterodimer alters gene transcription by binding to specific PPAR response elements in the promoter region of target genes (6), altering genes that control adipogenesis, lipid metabolism and glucose homeostasis (7). PPAR-gamma exists in two isoforms — PPAR-gamma1 and PPAR-gamma2 — as a result of promoter usage and alternative splicing (8). The PPAR-gamma1 isoform is expressed in many cell types, including adipocytes, osteoblasts, macrophages and muscle cells, while the PPAR-gamma2 isoform is restricted primarily to adipocytes (9).

EFFECT ON BONE METABOLISM IN VITRO

Osteoblasts share a common progenitor with adipocytes, as both are derived from marrow mesenchymal stem cells (10), and lineage-specific transcription factors are required for the commitment of the mesenchymal stem cells towards a specific lineage: PPAR-gamma2 for commitment towards the adipocyte lineage, and runt-related transcription factor 2/core-binding factor alpha-1 (Runx2/Cbfa1) for differentiation into osteoblasts (11). Lecka-Czernik and colleagues found that the activation of PPAR-gamma2 using rosiglitazone caused the differentiation of murine marrow-derived mesenchymal cells into adipocytes (12), but it has also been shown to irreversibly block cell differentiation into osteoblasts due to the suppression of Runx2/Cbfa1 (13). This impairment of osteoblast differentiation was shown through the suppression of osteoblast-specific proteins, including alkaline phosphatase, osteocalcin, osteopontin and alpha-1 (I)-procollagen (14).

PPAR-gamma may exert another effect on bone metabolism by inducing osteoclastogenesis. In vitro experiments have demonstrated that PPAR-gamma activation induces 1,25(OH)2D3-stimulated increases in receptor activator for nuclear factor kappa B ligand (RANKL) expression in mesenchymal cells through upregulation of RANKL mRNA expression (15). This, in turn, enhances osteoclast differentiation and increases the recruitment of osteoclast-committed precursors from the pool of hematopoietic cells (15).

These in vitro studies have demonstrated the effect of PPAR-gamma activation on the delicate balance between osteoblast and adipocyte differentiation, providing a possible mechanism by which TZDs may exert significant effects on bone metabolism, along with accompanying repercussions.

EFFECT ON BONE METABOLISM IN ANIMAL MODELS

Rodent models were initially used to investigate the possible relationship between TZD use and changes in bone metabolism. Rzonca and colleagues demonstrated a relationship between the use of TZDs and changes in bone mineral density, administering rosiglitazone to nondiabetic 6-month-old mice for 7 weeks, and comparing this group with mice fed the same weight of nonsupplemented chow (16). Dual energy X-ray absorptiometry (DEXA) analysis of total body BMD was performed at baseline and at 4 and 7 weeks after the initiation of treatment. The BMD measurements at 4 weeks post-treatment initiation did not show any difference, but at 7 weeks post-treatment initiation, a comparison of the absolute values of total-body BMD measurements demonstrated a significant difference between the rosiglitazone-fed group compared to the control mice (0.0462 ± 0.0001 vs. 0.0493 ± 0.0016 g/cm^2; $p<0.001$). At 7 weeks post-treatment initiation, there was an almost 10% decline in BMD in the rosiglitazone-fed group compared to baseline measurements ($p<0.001$). Similar results were seen in rats treated with pioglitazone (17). Such TZD-induced bone loss has also been associated with a decrease in the number of osteoblasts and an increase in the number of adipocytes in the bone marrow (18), resulting in changes in bone marrow structure and function, as well as bone microarchitecture (18). The data presented in these animal studies demonstrated that TZD use had a significant impact on changes in BMD. These results suggested that TZDs may have a similar effect in humans taking them for the treatment of type 2 diabetes,

and have served as the rationale for human studies to further investigate the relationship between TZD use, bone loss and the possibility of increased fracture frequency.

A recent study by Lazarenko and colleagues investigated the effect of rosiglitazone on the skeletons of growing, adult and elderly mice and found that absolute bone volume was significantly decreased in adult and elderly mice treated with rosiglitazone (15). The bone of young, growing mice was the least affected, but still incurred a statistically significant decline in bone formation (15). Bone microarchitecture was assessed using microcomputed tomography and bone histological examination, and investigators found that rosiglitazone induced changes resembling features commonly seen with aging, including decreases in bone volume fraction, decreases in trabeculae number and increases in trabecular spacing. These changes were seen in both the adult and elderly groups treated with rosiglitazone, while younger animals did not show changes in bone microarchitecture after treatment.

EFFECT ON BONE METABOLISM IN HUMANS

There have been limited data regarding the effect of TZDs on human bone metabolism, but more studies have shed light on this topic in recent months.

Schwartz and colleagues analyzed data from the Health, Aging and Body Composition (Health ABC) observational cohort study (19), which included 3075 participants ranging in age from 70 to 79 years at baseline; it included black and white people, men and women, and all participants were physically able. Both the prevalence of diabetes and use of TZDs were self-reported, and bone loss was assessed using changes in whole body, lumbar spine and total hip BMD over a 4 year period. Of the 666 people with diabetes in the study, 69 self-reported use of TZDs (22 troglitazone, 30 pioglitazone and 31 rosiglitazone). The study showed that each year of TZD use was associated with an additional –0.61% loss in total body BMD (95% CI –1.02, –0.21), an additional –1.23% loss in lumbar spine BMD (95% CI –2.06, –0.40) and a –0.65% loss in total hip BMD (95% CI –1.18, –0.12) (19). These data reflect BMD changes found in women treated with TZDs; no significant change in BMD was seen in men on similar treatment.

It is important to remember there are limitations to the studies investigating BMD in this population. DEXA is the current gold standard for assessing BMD and was used in the study described above. However, patients with type 2 diabetes generally have an increased body mass index, leading to an artificial increase in BMD score. As well, if bone marrow adiposity had increased, as hypothesized in patients treated with TZD, this would lead to an artificial decrease in BMD (20).

TZDS AND EFFECT ON BONE TURNOVER MARKERS

Recently, Grey and colleagues investigated the effect of treatment with rosiglitazone on bone turnover markers in women more than 5 years postmenopause and over the age of 55 (21). Exclusion criteria for the study included use of medications that affect BMD, BMD T-score $\leq$–2.5 at lumbar spine or total hip at baseline, contraindications to TZD or any other major systemic diseases. The study included 48 participants, with 24 randomized to 8 mg daily rosiglitazone for 14 weeks and 24 participants to placebo. The primary outcome of the study was biochemical markers of bone formation, with secondary outcomes being bone resorption markers and BMD. Investigators showed that in the rosiglitazone group, osteoblast marker procollagen type I N-terminal propeptide declined 13% ($p<0.005$ vs. placebo), and osteocalcin declined by 10% ($p=0.04$ vs. placebo). These changes were first evident 4 weeks after treatment initiation, and the results persisted for the length of the study. Total serum alkaline phosphatase also declined by 17% in the rosiglitazone group by the conclusion of the study ($p<0.001$ vs. placebo). On the other hand, beta-C-terminal telopeptide of type I collagen, a marker of bone resorption, did not change in response to rosiglitazone treatment ($p=0.9$ vs. placebo) (21). As a secondary outcome, BMD was measured at baseline and at the conclusion of the study. Total hip BMD declined by –1.9% in the rosiglitazone group, compared to a –0.2% decline in the placebo group ($p<0.01$ vs. placebo, 95% CI 0.6, 2.7). Lumbar spine BMD also fell by –1.2% from baseline in the rosiglitazone group ($p=0.02$ vs. baseline, SD=2.1), but lumbar spine BMD in the control group also declined by –0.2% ($p=0.7$ vs. baseline, SD=2.1), and the between-group difference was not statistically significant ($p=0.13$) (21).

TZDS AND EFFECT ON FRACTURES

Very little is known about the relationship between TZD use and new incidence of fractures; there is currently no trial that has investigated new onset of fractures as the primary outcome in relation to TZD use. Much of the information we have about this relationship comes from A Diabetes Outcome Progression Trial (ADOPT). The goal of this trial was to assess the efficacy of rosiglitazone compared to glyburide and metformin monotherapy in maintaining long-term glycemic control in type 2 diabetes, and patients were followed for a median of 4 years (22). The primary outcome was time from randomization to treatment failure, defined as fasting blood glucose (FBG) >10 mmol/L (180 mg/dL) after at least 6 weeks on the maximum indicated or tolerated dose of the study drug. Secondary outcomes included time from randomization to FBG >7.8 mmol/L (140 mg/dL) after at least 6 weeks on the maximum indicated or tolerated dose of the study drug, glycosylated hemoglobin (A1C), weight, measures of insulin sensitivity and beta-cell function. A total of 4360 patients were randomly assigned to the 3 treatment groups, and the study population consisted of patients between ages of 30 and 75 with FBG from 7.0 to 10.0

mmol/L (126 to 180 mg/dL) and with only lifestyle management as previous treatment. Among them, 1849 were women, the majority of participants were white, and the median age was 57 years. Incidence of fractures was not a specified outcome, but it was an unexpected adverse event identified through adverse event reports. Among the women in the rosiglitazone group, 9.3% reported any type of fracture during the course of the study, compared to 5.08% in the metformin group ($p<0.01$ vs rosiglitazone) and 3.47% in the glyburide group ($p<0.01$ vs rosiglitazone), corresponding to fracture incidence rates per 100 patient-years of 2.74 for rosiglitazone, 1.54 for metformin and 1.29 for glyburide (22). Further examination into the type of fractures incurred revealed that the rosiglitazone group had a significantly greater number of lower-limb fractures compared to the metformin ($p<0.05$) and glyburide groups ($p<0.01$), and a significantly greater number of upper-limb fractures compared to the glyburide group ($p<0.05$). There was no statistical significance regarding the number of vertebral or hip fractures between the 3 treatment groups. The results also did not reveal an increased risk of fractures in men treated with rosiglitazone.

Further information regarding the relationship between TZD use and fracture risk was presented by Takeda, the makers of pioglitazone, in a letter to healthcare providers. Analysis of Takeda's clinical trial database revealed that women in the pioglitazone group suffered 1.9 fractures per 100 patient-years, compared to 1.1 fractures per 100 patient-years in the comparator groups (placebo or another active agent). The majority of fractures were incurred in the distal upper limb (wrist, hand and forearm) or distal lower limb (foot, ankle, tibia and fibula). Like the results in ADOPT, there was no difference in fracture risk seen in men using pioglitazone.

These data would suggest an increased fracture incidence with TZD use in the range of 0.8 to 1.45 fractures per 100 patient-years. Expressed another way, treatment of 34 to 63 patients with a TZD for a 2 year period would cause 1 fracture (non-hip and non-vertebral). Such absolute risk calculations must be interpreted with caution, however, as none of these studies looked at fractures as a primary outcome measure, and so the data are at best hypothesis-generating. The fracture rates seen in ADOPT also seem to be somewhat higher than would be expected in that age group for all 3 medication intervention arms. A recent study estimated a fracture incidence of only 0.78 per 100 patient-years for women age 55, similar to the median age in the ADOPT study (24). Therefore, it is unclear to what extent the increased fracture risk in ADOPT is solely medication-related and to what extent type 2 diabetes itself may be adversely affecting bone in these patients.

RELATIONSHIP BETWEEN TYPE 2 DIABETES AND FRACTURE RISK

Patients with diabetes are already at increased risk for fractures. Patients with type 1 diabetes have been shown to have a lower BMD and an increased fracture risk (25). Several studies have found that patients with type 2 diabetes have an increased BMD (25), but paradoxically, these patients have a higher fracture rate (26).

The Women's Health Initiative Observational Study is a prospective study with the goal of identifying the predictors of morbidity and mortality in postmenopausal women (27). A total of 5285 post-menopausal women with type 2 diabetes were enrolled in the study, compared with 88,120 women without, and both groups had a mean age of approximately 64 years. As a primary outcome, all fractures and specific sites were measured. The study showed that the overall risk of fractures during the 7 year follow-up was significantly higher in the type 2 diabetes group, with a 20% higher risk of sustaining any fracture during the follow-up period, and an incidence rate of 2.86 fractures per 100 patient-years. In particular, hip, ankle, foot, upper arm, wrist and spinal fractures were significantly increased in the diabetes group compared to controls.

Earlier studies have also investigated the relationship between type 2 diabetes and fractures. The Study of Osteoporotic Fractures trial found a 30 to 39% increase risk of nonvertebral fractures, where rates of hip, proximal humerus, foot and ankle fractures were found to be statistically significant (28). Similarly, the Health ABC trial also found a 23% increase in risk of hip fractures (29). These studies indicate that there are factors other than BMD that contribute to the paradoxical increase in fracture risk found in type 2 diabetes patients.

The Rotterdam study also aimed to explore the relationship between type 2 diabetes, BMD and fracture risk in a group of 6655 patients (30). Both men and women were included in the study, which was limited to patients above the age of 55. This study also performed a subset analyses, using the glucose tolerance test to divide patients into newly diagnosed type 2 diabetes, already established/treated type 2 diabetes, IGT and normal glucose tolerance (NGT) groups. This study confirmed the results of prior studies by demonstrating that type 2 diabetes patients have an increased BMD, but also revealed that subjects with IGT also had a significantly increased BMD. The subgroup analysis revealed an increase fracture risk in the established/treated type 2 diabetes group compared to the NGT group. However, the subjects with IGT and newly diagnosed type 2 diabetes had a decrease in fracture risk compared to the NGT group. Since only patients with established/treated type 2 diabetes had a significantly increased fracture risk, the Rotterdam study indicated that the long-term complications and comorbidities of type 2 diabetes likely play a critical role in the development of fracture risk. Long-term type 2 diabetes complications include impaired vision, poor balance, peripheral neuropathy and cardiac disease, all of which can contribute to an increase risk of falling (31).

Another theory is that the quality of bone deposited by osteoblasts is inferior in type 2 diabetes. Long-term type 2 diabetes and subsequent hyperglycemia will cause an increase production of advanced glycation endproducts (AGEs). AGEs can deposit on the type I collagen network, which forms the building blocks of bone, thus leading to a decrease in tensile strength and increasing the risk of fracture (32).

CONCLUSION

Currently, rosiglitazone and pioglitazone are the 2 TZDs approved for use in the treatment of type 2 diabetes mellitus. Given the frequency with which TZDs are currently being prescribed in North America and that longstanding type 2 diabetes is associated with an increased risk of nonvertebral fractures, the relationship between TZD use and fracture risk needs to be clarified. The current evidence has shown an association between TZD use and changes in both BMD and bone turnover markers, but it is still unclear what its relationship is with fracture rate.

The ADOPT study shed some light on this area, but there are several limitations to the evidence presented by its investigators. First, fractures were not an expected adverse event, so that confounding variables such as pre-existing osteoporosis or its risk factors were not taken into consideration. Second, fractures were self-reported by study participants and were not screened for, so the actual incidence of fractures may have been significantly under-reported. Future research should include a randomized, controlled trial in which fracture incidence and type of fractures are prospective outcome measures.

Another question to address is whether the implementation of anti-osteoporosis therapy in this patient population is required for the primary prevention of future fractures. Osteoporotic fractures are an important and common cause of morbidity. Aside from the physical limitations and chronic pain suffered by these patients, fractures can often lead to significant emotional distress (33). Both hip and vertebral fractures are also associated with increased mortality. One prospective study found that women with clinical vertebral fractures had an 8.6-fold increase in 4 year mortality compared to control, and women with clinical hip fracture experienced a 6.7-fold increase in 4 year mortality (34). Although TZDs are very effective oral agents in the treatment of type 2 diabetes, clinicians need to consider fracture risk as a possible adverse event before initiating these agents, since fractures have such a significant impact on the patient's quality of life.

AUTHOR DISCLOSURES

No dualities of interest declared.

AUTHOR CONTRIBUTIONS

AL contributed substantially to conception and design, acquisition of data, analysis, and interpretations of data and wrote the first draft. WH contributed substantially to conception and design, acquisition of data and analysis, and revised it critically for important intellectual content, and gave final approval of published version.

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