Thiazolidinediones and bone fractures

The topic of increased risk of bone fracture associated with thiazolidinediones (TZD) treatment first drew international attention when a higher rate of fractures in women with diabetes treated with rosiglitazone was reported in the A Diabetes Outcome Program Trial (ADOPT)\(^1\). Subsequently, a number of clinical trials and observational studies addressing this issue have been reported and most of them have confirmed the increased risk of fracture in elderly women with type 2 diabetes mellitus treated with both rosiglitazone and pioglitazone. A recent report by Bilik et al. provided additional insight into the association between TZD treatment and bone fractures in patients with type 2 diabetes mellitus, showing that postmenopausal women taking TZD and the subset of men taking both loop diuretics and TZD were at increased risk for fractures\(^2\). Nevertheless, the results of currently available reports have still been inconclusive. For example, rosiglitazone and pioglitazone were shown to have comparable risk of fractures in some studies, whereas others have found a difference in the risk of fracture between these two drugs. Does the risk for fracture with TZD extend to men and to younger patients? Is it also applicable in Asian populations?

TZD exert many metabolic actions by interaction with peroxisome proliferator-activated receptor (PPAR\(\gamma\)), which is expressed in a number of tissues and directly regulates gene expression involved in adipogenesis, glucose homeostasis and inflammation responses. Most importantly, PPAR\(\gamma\) plays an important role in adipocyte differentiation, as shown by studies in which overexpression of PPAR\(\gamma\) in fibroblast cell lines initiates adipogenesis, and embryonic stem (ES) cells and embryonic fibroblasts from PPAR\(\gamma\) deficient mice could not differentiate into adipocytes.

A series of experiments, in which TZD were given to rodents, showed adverse effects of TZD against bone metabolism. Both rosiglitazone and pioglitazone have been shown to consistently cause bone loss accompanied by decreased osteoblast activity and bone formation, and often by an increase in bone marrow adiposity. Although the effects of TZD administration on bone resorption were somewhat inconsistent and less compelling, increased bone resorption was often concomitant with decreased bone mass, particularly in aged animals given rosiglitazone. TZD are likely to have suppressive effect on bone formation and their stimulatory effects on bone resorption might be enhanced when given to aged animals (Figure 1).

At a cellular level, a number of signaling pathways mediated by TZD might indirectly influence bone metabolism. Amelioration of insulin resistance by TZD lowers circulating levels of insulin and amylin, each of which is anabolic to osteoblasts. Activation of PPAR\(\gamma\) in adipocytes influences expression and production of an array of adipocytokines, many of which have been suggested in the regulation of bone metabolism. Rosiglitazone is reported to decrease circulating insulin-like growth factor (IGF)-I level, which is one of the crucial factors in the regulation of osteoblast differentiation and proliferation. Decrease in IGF-I in bone might be detrimental to bone mass through the inhibition of osteoblast formation. Thus, many humoral factors, under the regulation of TZD, are likely to modulate bone metabolism concurrently with improvement of insulin resistance.

A report of increased risk of fracture with TZD treatment in the ADOPT study\(^3\) was subsequently followed by

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Figure 1 | Effect of thiazolidinedione on bone metabolism. The activation of peroxisome proliferator-activated receptor (PPAR\(\gamma\)) by thiazolidinedione (TZD) stimulates adipogenesis, thereby regulating a number of cellular signaling pathways involved in bone metabolism. Differentiation of mesenchymal stem cells into osteoblasts is affected by preferential differentiation of mesenchymal stem cells into adipocytes. Reduced osteoblastogenesis likely indirectly modulates osteoclastogenesis. Altered maturation of mesenchymal stem cells, in concert with humoral factors, shifts the balance between bone formation and resorption.
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