

# Local and systemic functions of bone fat and its contribution to the energy metabolism – The effect of diabetes and obesity on bone

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**Keywords:** Bone, Fat, Adipokines, Diabetes, Thiazolidinediones, PPAR $\gamma$

Osteoporosis, diabetes and obesity are major public health concerns due to their prevalence in economically developed countries. The current estimates and the future prognosis for the occurrence of these diseases in the United States are alarming and indicate that 40% of the population are obese, 20% of elderly individuals are osteoporotic and almost 8% of the population are diabetic. Thus, the economic burden to treat these diseases is very high and it will be rising. New clinical evidence indicates that diabetic patients have increased fracture risk as compared to non-diabetics. In addition, a class of anti-diabetic drugs, thiazolidinediones (TZD), causes bone loss and further increases fracture risk in diabetic individuals. A number of evidence indicates that osteoporosis, obesity and diabetes share several features including genetic predispositions, molecular controls and a common cell progenitor.

The peroxisome proliferator-activated receptor-gamma (PPAR $\gamma$ ) transcription factor is a DNA-binding nuclear receptor, which regulates glucose metabolism, energy expenditure, fat development and bone mass. In bone, PPAR $\gamma$  controls lineage commitment of multipotential marrow mesenchymal stem cells (MSC) toward bone forming cells (osteoblasts) and fat cells (adipocytes). Specifically, PPAR $\gamma$ 2 isoform acts as a positive regulator of adipocyte differentiation and a dominant-negative regulator of osteoblast differentiation<sup>1</sup>. PPAR $\gamma$  is also expressed in hematopoietic cells and controls osteoclast differentiation<sup>2</sup>. With aging bone

marrow undergoes structural and functional changes, which lead to decreased number of osteoblasts, increased number of osteoclasts and increased number of adipocytes. These changes result in a loss of bone and an accumulation of fat in bone. PPAR $\gamma$ 2 expression increases in MSCs with aging and aging bone is more susceptible to the loss due to a therapeutic treatment with anti-diabetic thiazolidinediones (TZD), which are specific agonists for this nuclear receptor<sup>3,4</sup>.

Although bone fat occupies a significant amount of space in the bone cavities of the adult skeleton, its function in glucose and fatty acid metabolism is largely unknown. Marrow adipocyte differentiation is controlled by the same mechanisms as white and brown fat adipocytes and includes common phenotype-specific transcription factors. Moreover, marrow adipocytes express a similar set, as extramedullary adipocytes, of genes involved in lipids and carbohydrates metabolism. In addition, bone fat produces adipocyte-specific hormones (adipokines) such as leptin, adiponectin and resistin. These hormones are involved in the regulation of energy metabolism and represent hallmarks of endocrine activity of extramedullary fat depots from which they are released to the circulation. Marrow MSCs express receptors for adiponectin and leptin and osteoblast differentiation is regulated by these hormones. These together suggest that adipokines produced in marrow may have a local function in bone, as well as they may contribute to the regulation of energy metabolism in peripheral tissues if released to circulation.

Insulin has an anabolic effect on bone and insulin receptors are expressed in MSCs, however very little is known about bone cell sensitivity to insulin and especially whether bone develops insulin resistance. Lack of insulin in diabetes type I is associated with a low bone mass, whereas hyperinsulinemia in diabetes type II is associated with higher bone mass. Interestingly however, insulin resistant T2D patients lose more bone with aging and have increased bone fractures risk as compared to non-diabetic controls<sup>5,6</sup>.

The author has no conflict of interest.

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Accepted 11 August 2008

If bone is a part of the energy metabolism system then it should be considered as a target for anti-diabetic therapies. We and others have demonstrated that clinically approved TZDs have an adverse effect on bone and cause bone loss and fat accumulation in bone<sup>7-9</sup>. An analysis of PPAR $\gamma$  transcriptome of marrow adipocytes clearly shows that these cells, similarly as adipocytes from other fat depots, upon TZDs treatment acquire a favorable profile in respect to insulin sensitivity, and lipids and carbohydrates metabolism. This, together with the finding that pro-adipocytic and antiosteoblastic activities of PPAR $\gamma$  can be separated by using ligands of different chemical structures<sup>10,11</sup>, indicates a possibility to stimulate one (e.g., anti-diabetic) PPAR $\gamma$  activity without stimulating another (e.g., anti-osteoblastic) activity. Thus, studies to elucidate PPAR $\gamma$  bone-specific activities are the groundwork for the development of PPAR $\gamma$  selective modulators, which will be both beneficial for the treatment of diabetes and safe or even beneficial for bone.

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