**The Impact of Diabetes on Bone Metabolism and Fracture Risk**

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**Keywords**

Osteoporosis; Fracture Risk; Diabetes Mellitus; Pathogenesis; Underlying Mechanism; Treatment

Osteoporosis has been known for decades as a silent epidemic, so widespread that affect about 50% of the elderly. From diabetes mellitus (DM) or pre-diabetes, suffer up to 20% of the some populations. These two diseases often coexist in patients and contribute to the complexity in the treatment of these patients. It has been known earlier that DM patients have an increased fracture risk, but for a long time it was meant that the cause of increased fracture risk was just an increased risk of falls, frequent hypoglycemia and an older age. However, the latest research and meta-analysis indicate new aspects and interaction between bone metabolism and glycoregulation, both in type 1 (T1DM) and in type 2 DM (T2DM). It is known that normal and even elevated bone density values can be observed in patients with T2DM, with commonly used bone mineral density methods such as densitometry. However, despite preserved bone density, patients with T2DM have an increased risk of fractures. Even the patients with HbA1c level of 7.5%, and higher BMD have increased risk of all types of fractures. US and Europe studies revealed that T2DM patient have over two-fold increase in risk of hip fractures in men and women and these risk are even more noticeable in man. T1DM patient have slightly reduced bone mineral density and a far more pronounced fracture risk, as high as 6.9 fold higher for hip fracture [1, 2].

The mechanism of the appearance of bone fragility can be the result of many pathophysiological events in bones in patients with DM. Up regulation of PPAR-γ, tumor necrosis factor-α (TNF-α), fatty acid binding protein and increased adipocyte formation from mesenchimal stem cells seen in DM could be the cause of the lipid deposits in the bone marrow, marrow cavity expansion, decrease in bone microcirculation, and the reduction of number of osteoblasts available for bone formation. When glycoregulation worsens, the levels of osteocalcin in bone and serum are lower, and the osteocalcin itself is incompletely carboxylated that negatively affects glucose control and energy metabolism. Recent studies shown attenuation of bone turnover in patients with T2DM. Higher levels of sclerostin, an inhibitor of the Wnt/β-catenin signaling pathway found in T2DM patients is negatively correlated with bone turnover markers and can be responsible for decreased bone formation. In both types of DM, advanced glycation end products (AGEs), interferes in forming additional cross links between collagen fibers in bone resulting in increased stiffness but also in increased fragility of bone tissue. All above mentioned mechanisms leads to a reduction of bone turnover, which consequently leads to the formation of, in T2DM maybe denser, but qualitatively inferior bone tissue [1, 3, 4].

Older age, the existence of chronic degenerative complications such as retinopathy and neuropathy, and the risk of hypoglycemia increase the risk of falls and, consequently, the risk of fractures. When considering the presence of increased bone fragility in DM patients, it is not surprising that the fracture risk in DM patients is significantly higher.

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**Received** August 23, 2017; **Accepted** August 23, 2017; **Published** September 12, 2017

**Citation:** Tijana Icin (2017) The Impact of Diabetes on Bone Metabolism and Fracture Risk. SF J Orthopedic Rheumatol 1:1.

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DM therapy uses a wide range of medicines. For some, such as thiazolidinediones (TZDs), it is known to negatively affect bone metabolism, causing a decrease in bone density and increase in fracture risk. Patients with insulin therapy have a higher risk of hypoglycemia, which contributes to a higher risk of fall and fracture incidence. In contrast to these drugs, DPP-4 inhibitors have been shown to have a beneficial effect on bone metabolism by improving bone mineral density, bone quality, and bone markers. There is some evidence that GLP-1 receptor agonist can promote bone formation, reduce bone resorption and leads to balance in bone turnover. Metformin was also associated with a reduction in the risk of fractures [5, 6, 7]. Based on these new insights there is recommendation that metformin, sulfonylureas, DPP-4 inhibitors and GLP-1 receptor agonists, should be the preferred treatment for T2D in patients who also have osteoporosis [8].

The question arises when it is necessary to start a treatment in patients with DM in order to reduce fracture risk. Most recommendations for the treatment of osteoporosis are based on bone mineral density or fracture risk assessment via FRAX referrals that do not take into account an increase in fracture risk in DM patients with normal or even higher BMD. It is also questionable whether the choice of therapy in patients with DM is the same as in other patients with osteoporosis. New drugs, such as anti-sclerostin antibodies, could theoretically have a favorable effect on the underlying mechanism of bone fragility in patients with DM. Further research is needed to provide answers to these questions [9].

References