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THE EFFECT OF OBESITY ON BONES

Epidemy of obesity is followed and associated with epidemy of type 2 diabetes mellitus (T2DM). Patients with T2DM are at significant risk for development of micro and macrovascular complications but they are also at significant fracture risk. Fracture risk is almost two times higher in T2DM subjects compared to non-diabetics, both men and women (1).

Significant risk factors are high prevalence of peripheral neuropathy and retinopathy (reduced vision), hypoglycemia, orthostatic hypotension, TIA/stroke, diabetic foot, nocturia and cognitive dysfunction that lead to falls. On the other hand, 90 % of patients with T2DM are obese and have normal / increased bone mineral density (BMD). It was previously shown that low body mass index (BMI) is risk factor for fracture while obesity was assumed as protective factor for fractures (2, 3). Body weight is associated with BMD and many obese patients have relatively higher BMD and bone strength. Reasons for this finding are many such as greater mechanical loading on bones. Meta-analysis of prospective cohort studies suggested that overall obesity significantly decreases the risk of hip fracture in adults, and that obesity is probably a protective factor of hip fractures (4). One of the specific reasons for hip protection is increased soft-tissue padding. Accumulation of fat mass in hip region (gluteofemoral adipose tissue) reduces impact forces when they fall and therefore reduce risk for hip fracture (5).

Is it possible that T2DM is so powerful factor that makes such difference between obese patients with T2DM who are at 2 times higher risk for fractures and obese patients without T2DM who are protected from fractures?

The main effect of hyperglycemia and insulin is accumulation of AGEs in collagen fibers inhibiting type 1 collagen synthesis. It favors formation of weak

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bridges between collagen fibers that subsequently alters structure and strength of bones. Also, hyperglycemia has negative effect on the expression and secretion of osteocalcin (OC) (6). One of the main suggestions is that increased fracture risk in T2DM is due not to reduced BMD but impaired bone quality.

At the same time, low osteocalcin levels and cytokine-induced osteoclast activity can be observed in obese insulin-resistant patients without T2DM. Bone specific hormone osteocalcin (OC) positively correlated with osteoblast activity in the process of new bone formation. Its secretion is regulated by insulin, leptin, adiponectin and sympathetic tonus (7). OC levels are in negative correlation with hepatic and peripheral insulin resistence, while there is positive associations with insulin secretion and beta-cell mass. In vitro studies demonstrated that OC administration improves insulin sensitivity, insulin secretion and GLP-1 secretion (8). In humans obese and overweight patients had lower OC levels than normal weight adults. Also patients with type 2 diabetes mellitus (T2DM) had lower levels than patients with impaired and normal glucose tolerance (9). In young adults OC inversely correlated with BMI and waist circumference, systolic blood preassure, IL-6 and insulin resistance, while there was positive correlation with adiponectin levels (10).

There are also other factors observed in obesity that has impact on bone quality such as vitamin D deficiency and secondary hyperparathyroidism, calcium malabsorption, hypogonadism, muscular impairment, comorbidities and comedications.

More recently, new data shown that obesity is protective for hip and pelvis fractures but on the other hand it is associated with increased risk for fractures of proximal humerus, upper leg and ankle fractures (11, 12, 13).

Further analysis demonstrated that obese patients with predominant abdominal obesity are even at increased risk for hip fracture. Meta-analysis demonstrated linear relationship between waist-hip ratio and the risk for hip fracture: for each 0,1 increment of waist-hip ratio the risk for hip fracture increased about 3,0% (especially within range 0,77-0,92). The risk for hip fracture was increased with the increase od waist circumference, also. Adults with waist circumference of over 105 cm had 55% increased risk of hip fracture in comparison to adults with waist circumference up to 80 cm. Reasonable explanations might be abdominal obesity related insulin resistance and chronic inflammation that stimulates bone resorption and suppress bone formation as

previously mentioned. Another important point is that increased body size in abdominal region increases mechanical instability and risk for fall. These findings suggest that hip circumference might be a protective factor (14).

These findings rise particular concern that DEXA scan overestimate BMD values due to excess fat tissue, especially at axis sites. Therefore, quantitative computerized tomography at peripheral sites (pQCT) that is less affected by thickness of fat was done. Results suggested that obese postmenopausal women had higher BMD and higher values cortical and trabecular architecture and calculated bone strength in comparison to normal weight postmenopausal women. But after normalization for body weight all the bone parameters were significantly lower in obese women, such as approximately 20% lower BMD at the spine and hip. (15).

Although BMD is significantly higher in obese women with fractures than in their nonobese counterparts, obese women with fracture have a significantly lower BMD at both the lumbar spine and femoral neck when compared with women of similar age and weight without fractures. These findings suggest that BMD may be inappropriately low in those obese subjects who fracture and also confirms the importance of BMD evaluation in obese individuals. How-ever, since obese individuals generally have higher BMI and BMD, fracture algorithms such as FRAX might be expected to underestimate fracture probability (16).

In conclusion, obese individuals has increased risk for fractures despite normal/increased BMD. The main reasons for this observation is reduced bone quality and mechanical factors (instability and impact forces during fall).

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