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Bone and Glucose Metabolism Anomalies: A Package of Two

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ABSTRACT

The diabetes bone disease is a dynamic new dynamic concept accompanying many others complications of diabetes. The underlying mechanisms are related to the quality damage of the bone because of advanced advanced glycation end products, trabecular anomalies, increased cortical porosity, low bone remodelling markers status, inflammation, potential links to persistent hypercortisolema and vitamin D status impairment. Thus one disease as diabetes mellitus brings a package of a second anomaly at the skeleton level.

KEYWORDS : bone, diabetes mellitus, osteoporosis

Introduction

The diabetes mellitus (especially type 2) has an increasing frequency during the last decades. The diabetic skeleton disease is a relative new and dynamic concept. We aim to point the underlying mechanisms of diabetic osteopathy.

General data: pathogenic mechanism of bone anomalies

The bone quality is the major factor causing fractures in diabetic population. The qualitative parameters cause the bone fragility which is probably the pathogenic core of the diabetic bone disease. **(1)** In both types of diabetes the structure of bone is altered, including the micro architecture and the quality of collagen for instance the intermolecular cross-linking which offers strength. Because of the advanced glycation end products the useful collagen cross-links (enzymatic both immature divalent and mature trivalent) are replaced by non useful as nonenzymatic cross-links as a result of glycation and oxidation correlated to high levels of blood glucose and elevated oxidative stress. **(2)**

Mouse type 2 diabetic KK-Ay models (Yellow Kuo Kondo) displayed a trabecular thickness and trabecular volumetric bone mineral density lower than control, negatively correlated to the glucose metabolism control. Also in this model an up-regulation of the bone cells genes (as for type 1 collagen, osteocalcin, osteonectin coming from osteoblats and TRAP coming from osteoclasts) was registered associated with high levels of insulin. **(3)** The major clue in bone quality alteration is the finding that there is an elevated cortical porosity in type 2 diabetes. **(4)**

In humans the bone mineral density as assessed by Dual-Energy X-Ray Absortimetry (DXA) examination is low in type 1 and high in type 2 diabetes, many mouse models have similar changes. For instance, the KK/UpjAy/J mouse model for type 2 diabetes presents in concordance with glucose metabolism anomalies elevated fat pad weight, decreased femoral and tibial mineral density, altered synthesis and function of osteoblasts and osteoclasts (based on alkaline phosphatase activity and TRAP staining), impaired mechanical properties of the tibia. **(5)** In both obese and type 2 diabetic rat models as Wistar fatty rat or Zucker diabetic fatty (ZDF) rat together with the pancreatic, renal, nerves, and retinal anomalies, there were discovered decreased osteogenesis and impaired bone mineral density. **(6)** Using the animal models has many advantages but in the particular case of type 2 diabetes mellitus the rodent models display many of the bone disturbance as humans but the potential confounders factors are the fact that diabetes is usually registered before the complete skeleton maturation so the peak bone mass is not properly achieved and thus the bone mineral density might remain low in contrast to what happens in people with type 2 diabetes. **(7)**

The bone turnover markers are low in type 2 diabetes mellitus. A controlled study in 1410 menopausal type 2 diabetic Chinese subjects found suppressed levels of β-CTX (serum C-terminal telopeptide of type I collagen) and P1NP (serum N-amino terminal prepeptide of type 1 procollagen) and non-decreased bone mineral density at DXA, as one of the mechanisms related to the fracture risk independently of bone density. **(8)**

Enteric hormone as GLP-2 (Glucagon-like peptide 2) seems to modulate the bone markers in response to food. A study in menopause including women already diagnosed with type 2 diabetes found that a part from blunted bone turnover markers at baseline they have an abnormal response after the meal while GLP-2 is increased suggesting a correlation between the food intake and the skeleton remodelling status. **(9)** The connection between glucose anomalies and bone is also possible via the nutrition. Observations in streptozotocin - induced diabetic rats under l-arginine supplements or soy enriched diet for 3 months revealed that both normalized parathormon levels and increased the serum bone formation marker osteocalcin, as well as they had lower levels of bone resorption markers and cathepsin K levels, suggesting the potential control of skeleton disease via adequate nutrition. **(10)**

An important element of bone dysfunction is the chronic inflammation which has an age-dependent pattern augmented in type 2 diabetes mellitus at older ages. The inflammation associated cytokines also cause calcium metabolism disturbances as vascular calcifications being displayed as a severe form of atherosclerosis. **(11)**

The type 2 diabetes mellitus mostly associates metabolic complication as obesity, arterial hypertension, hyperlipemia, high uric acid, and increased inflammatory status. A recent study in a German population if 2685 persons pointed a correlation between visceral and abdominal adipose tissue (a magnetic resonance imaging analysis) and the risk fracture as predicted by quantitative ultrasound stiffness parameter. **(12)** There is persistent hypercortisolemia that may damage the skeleton integrity connected to the metabolic pattern as seen in type 2 diabetes. A case-control study in menopausal diabetic women pointed a higher prevalence of X-ray detected vertebral fractures (p value=0.031), a higher level of plasma cortisol after low dose of dexamethasone suppression test (p value=0.01), and also an increased prevalence of sensitizing N363S SNP (single-nucleotide polymorphisms) glucocorticoid receptor but in women with fractures versus those without fractures regardless diabetes (similar p value=0.02). **(13)**

Type 1 diabetes mellitus has been associated with bone anomalies since several years. The osteoblasts differentiation is blunted because of high advanced glycation end products. The risk of falls is increase because of the hypoglycaemia episodes and neuropathy. Overall, there is a 6.9-fold higher hip fracture risk. **(14)** The osteocalcin, a bone formation markers originating from osteoblasts is implicated in glucose setup and energy expenditure by feedback from bone to brain. In one cross-sectional study on type 1 diabetic subjects there was a relevant inverse correlation between the remodelling marker and the values of hemoglobin A1c, respective the body mass index, confirming the osteoblast damage in case of poor glucose control.

(15) The damage of the bone is also caused by the high glucose input itself. In vitro studies (preosteoblastic cell line MC3T3-E1) and in vivo (diabetic mouse model) revealed that exposure to glucose excess decreases both osteoblast viability and differentiation via modulation of microRNA-378 that activates by signalling PI3K/Akt and targeting caspase-3 (CASP3). **(16)**

In both types of diabetes the vitamin D status is impaired. The immune component of type 1 is correlated with autoimmune diseases as celiac disease associated with vitamin D deficit. In type 2, there are many studies pointing a correlation between diabetes, obesity, metabolic syndrome and hypovitaminosis D. Yet, a high prevalence of D vitamin deficit is registered in menopause regardless the metabolic pattern. **(17)** On the other hand, the vitamin D modulates the insulin resistance and the function of pancreatic β cells, inhibits fat deposits formation and reduces the hunger offering a support in obese diet and glucose metabolism control. **(18,19)** Some suggested that decreased vitamin D is caused by obesity (not vice versa) but this is still a matter of debate**. (19)** The vitamin D receptor polymorphism was also found in relationship to diabetes. A transversal study in Saudi Arabian population (285 with metabolic syndrome including type 2 diabetes mellitus and 285 controls) found that obesity, type 2 diabetes and HDL cholesterol is correlated to vitamin D receptor polymorphism. ApaI SNPs (single nucleotide polymorphisms) increase the risk of hypovitaminosis D in diabetics**. (20)** Studies with others potential osteoporosis gene related polymorphisms as low-density lipoprotein receptor related protein 5 (LRP5) were not conclusive for the diabetic osteopathy**.** (21)

Conclusion

A complex panel of mechanisms are associated in diabetes associated bone anomalies from damage in bone micro-architecture to inflammation, and low bone remodelling markers.

Conflict of interest: none

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