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BONE METABOLISM DISORDERS DURING DIABETES MELLITUS

Abstract

Long-term exposure to a diabetic environment leads to changes in bone metabolism and impaired bone micro-architecture through a variety of mechanisms on molecular and structural levels. These changes predispose the bone to an increased fracture risk and impaired osseus healing. In a clinical practice, adequate control of diabetes mellitus is essential for preventing detrimental effects on bone health. Alternative fracture risk assessment tools may be needed to accurately determine fracture risk in patients living with diabetes mellitus. Currently, there is no conclusive model explaining the mechanism of action of diabetes mellitus on bone health, particularly in view of progenitor cells. In this review, the best available literature on the impact of diabetes mellitus on bone health in vitro and in vivo is summarised with an emphasis on future translational research opportunities in this field.

Keywords: *diabetes mellitus, bone metabolism, fracture, lymph drainage, bone disorders*

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Şəkərli diabet zamanı sümük metobolizm pozulmaları

Xülasə

Şəkərli diabet zamanı sümük metabolizmasında dəyişikliklər və molekulyar həmçinin struktur səviyyələrdə çoxlu mexanizmlər vasitəsilə sümük mikroarxitekturasının pozulması meydana çıxır.

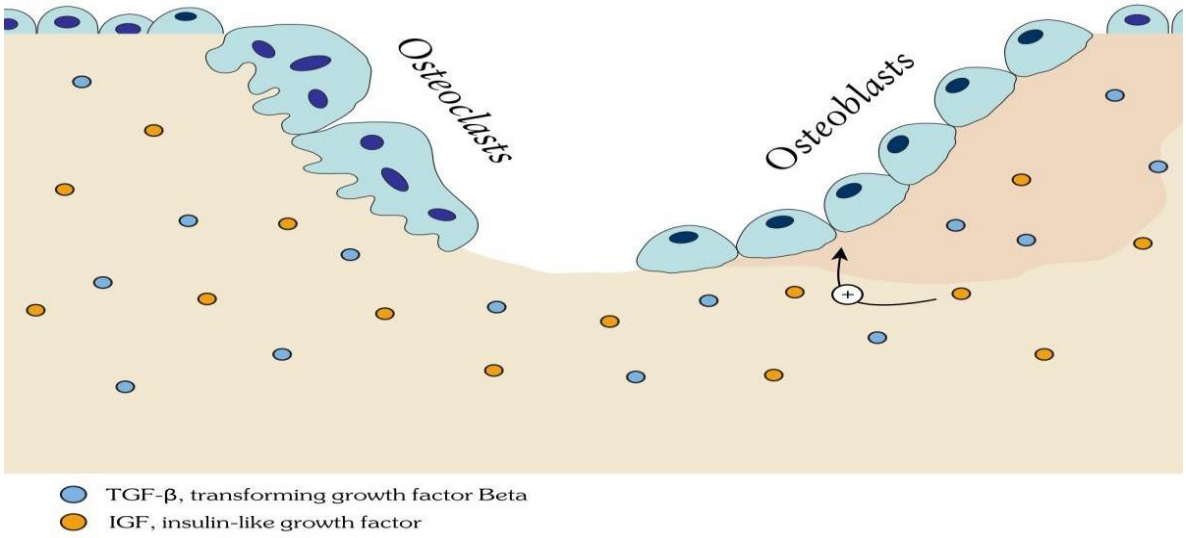
Bu dəyişikliklər sümükdə sınıq riskinin artmasına və sümük toxumasının pozulmasına səbəb olur. Klinik praktikada, sümük sağlamlığına zərərli təsirlərin qarşısını almaq üçün şəkərli diabetin adekvat nəzarəti vacibdir. Diabetik xəstələrdə sınıq riskini dəqiq müəyyən etmək üçün alternativ sınıq riskinin qiymətləndirilməsi alətlərinə ehtiyac ola bilər. Bu icmal şəkərli diabetin

sümük sağlamlığına təsiri ilə bağlı ən yaxşı mövcud ədəbiyyatı in vitro və in vivo olaraq ümumiləşdirir və bu sahədə gələcək tədqiqatlar üçün potensiala diqqət yetirir.

Açar sözlər: *şəkərli diabet, sümük mütobolizmi, sınıq,limfa drenaj,sümük pozulmaları*

Introduction

The relationship of diabetes mellitus (DM) with disorders of bone metabolism and tissue lymph drainage is not yet fully understood. While type 1 DM (DM1) is characterized by a decrease in bone mineral density (BMD), in type 2 DM (DM2) in a number of studies, there is no decrease in BMD or there are higher rates compared to controls. At the same time, in DM2, as in DM1, there is a high risk of fractures, which indicates a deterioration in quality? bones in diabetes. This article discusses various mechanisms of bone tissue damage in DM, as well as possible causes of differences in the severity of bone disorders in DM1 and DM2. Considering the high risk of foot fractures in patients with DM, special attention is paid to distal neuropathy as a possible factor that worsens the condition of the bone tissue (1). The diabetes mellitus (DM) pandemic was mostly related to the growing incidence of bone



metabolism tissue lymph drainage worldwide.

Diabetes mellitus refers to a group of diseases that affect how the body uses blood sugar (glucose). Glucose is an important source of energy for the cells that make up the muscles and tissues. It's also the brain's main source of fuel.

Chronic diabetes conditions include type 1 diabetes and type 2 diabetes. Potentially reversible diabetes conditions include prediabetes and gestational diabetes. Prediabetes happens when blood sugar levels are higher than normal. But the blood sugar levels aren't high enough to be called diabetes. And prediabetes can lead to diabetes unless steps are taken to prevent it.

Thus, DM-induced bone fragility was recently reported as a diabetic complication. This disorder needs to be identified and diagnosed early and adequately to avoid more symptoms and impairments. Bone weight is lowered and the risk of fractures rises in type 1 diabetes mellitus (T1DM). However, type 2 diabetes mellitus (T2DM) will increase bone density per se because of the elevated chance of fracturing. This indicates that bone consistency plays an important part in the pathogenesis of diseases. This research is aimed at defining the function of advanced glycation end-products (AGEs), micro-architectural changes, and altered bone turnover. The risk of fracture can be varied by drugs used for treating DM. Thiazolidinedione exacerbates bone degradation, for example, which raises the risk of fractures, particularly in older females. In contrast, metformin and sulfonylureas appeared to have no adverse effects on bone health and could guard against fragility. Evaluating bone mineral density (BMD) and other risk factors may

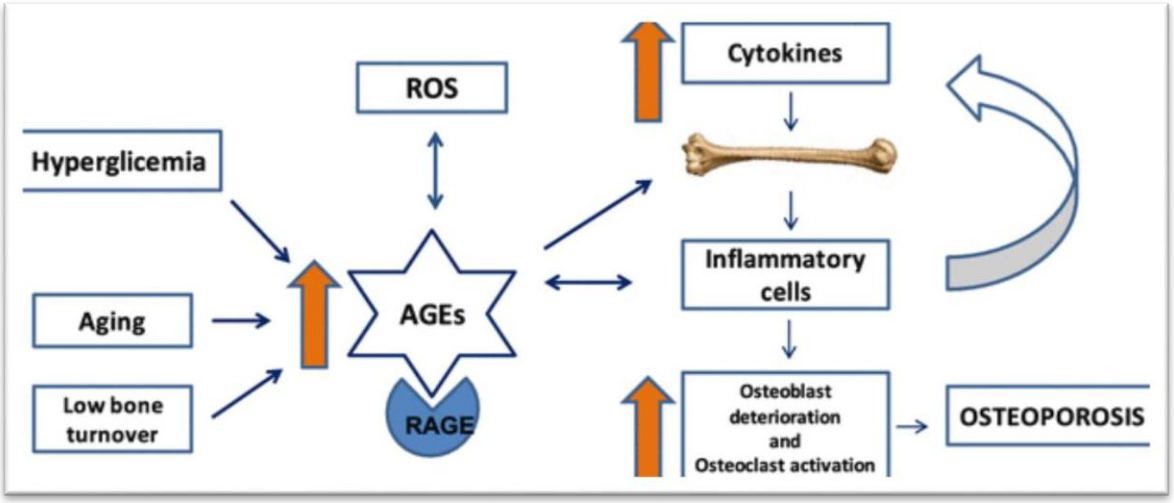
aid in developing tailor-made recovery plans as part of the diagnostic process. Increased osteoporosis awareness is important, considering the increasing and older population of DM patients.

Diabetes and osteoporosis are common diseases and can occur at the same time. Studies have shown that osteoporosis and diabetic fractures are more likely than chance can expect (Starup-Linde, Vestergaard, 2015:93-99). Osteoporosis is a bone disorder characterized by a decline in the overall consistency of the bone and may eventually lead to an increased risk of fractures. With age, the prevalence of osteoporosis continues to increase. Osteoporosis-related fractures have affected people above the age of 50, one-third of the female population, and one-fifth of the male population (Starup-Linde, Vestergaard, 2015:93-99). Diabetes mellitus, more commonly called diabetes, is a debilitating, long-term (or 'chronic') disease that occurs when glucose levels increase in a person's blood because their body is unable to produce any or enough of the hormone insulin, or are unable to use the insulin it produces effectively (Aung, Amin, Gulraiz, Gandhi, Pena Escobar, Malik, 2020:12). There are currently an estimated 463 million diabetic adults aged 20-79 years. This age group comprises 9.3% of the world population. The total figureis expected to rise up to 578 million (10.2%) by 2030 and by 2045 to 700 million (10.9%) **(**Aung,Amin, Gulraiz, Gandhi, Pena Escobar, Malik, 2020:12). Diabetes influences the functioning of many organs in the human body, including the heart, brain, kidneys, peripheral nerves, eyes, and feet. Researchers have generally accepted findings regarding the association between diabetes and osteoporosis over recent years. Both diabetes and osteoporosis are metabolic disorders with a complicated relationship (Napoli, Chandran, Pierroz, Abrahamsen, Schwartz, 2017:208-219).

Additionally, there can also be more than 100 kinds of complications involved in the disease, and it is currently known as the disease with the most complications (Napoli, Chandran, Pierroz, Abrahamsen, Schwartz, 2017:208-219).

In spite of its effects on fractures, diabetes is one of the most severe comorbidities, as suggested by studies in the USA and Europe. The presence of diabetes is individually related to an increased risk of fracture, owing to bone growth and strength improvements; the risk of hip fracture is nearly twice as high for diabetes patients as for people without diabetes (Sato, Ye, Sugihara, Isaka, 2016:489). Accumulated evidence has demonstrated that the risk of osteoporotic fractures with both T1DM and T2DM is considerably greater. A previous meta-analysis showed that in DM elevated probabilities of any fracture (relative risk (RR) 1.32), hip (RR 1.77), upper arm (RR 1.5), and ankle fractures (RR 1.24), with no effect on distal forearm (RR 1.02) and vertebral fractures (RR 1.56). Besides, the frequency of fractures in patients with T1DM was greater than T2DM at overall 1.24 fold, hip 3.43 fold, and ankle fracture 1.71 fold. However, no other variations among subgroups established the relationship of DM with the upper arm, ankle, vertebrae, and complete fractures differed by sex, nature of the study, and region (Wang, Ba, Xing, Du, 2019;9). An additional meta-analysis found a risk of hip fracture up to 6.3 times and
1.7 times higher than the non-diabetic trials of T1DM and T2DM patients, respectively. In patients with diabetes, there has been a 2.03-fold more severe risk of vertebral fracture than in non-diabetes controls. Based on a review in the integrated analysis of three large prospective future trials, the femoral neck bone mineral density (BMD) with the possibility of hip fracture was 0.59 and 0.38 higher than in non-diabetic controls for women and men with diabetes, respectively (Yuhao, Cenyi, Yang, Guihua, Yong, 2019:1203-1214). There have been repeated recordings of Japanese men and women with T2DM an alternate vertebral fracture risk factor after age transition, lumbar BMD, and body mass index (odds ratio, men 4.7, and women 1.9) (Kanazawa, Sugimoto, 2018:2773-2785). In diabetic patients, the pathogenesis of bone quality change is most likely multifactorial: 1) deposition of advanced glycation end-products (AGEs) in the bone matrix, 2) micro-architectural changes and bone strength, and 3) serum bone turnover markers are considered necessary.

The bone matrix includes abundant collagens of type 1, and by forming physiological crosslinks between collagen fibers, bones can retain their flexibility and strength. AGEs are formed by the parallel, nonenzymatic chemical glycoxidation of amino protein groupings.



When patients have diabetes, AGEs are formed non-physiologically. However, several studies have demonstrated a considerably higher serum AGE rate in diabetic patients than in non-diabetic (Yoshida, Okumura, Aso, 2005:345-350). With age, AGEs are known to build up in various tissues, including atherosclerotic plaques in the coronary artery, kidney, brain, and bone. A well-characterized AGE product, pentosidine is a good indicator of microvascular and macrovascular problems in diabetic patients (Grandhee, Monnier, 1991:11649-11653). The quantity of bone pentosidine is linked to the strength of the human spine, irrespective of BMD (Yoshida, Okumura, Aso, 2005:345-350). Increased serum pentosidine, AGEs, and soluble receptors of AGE (sRAGE), compared with the control group with T2DM, have been recorded. These findings suggest that variables related to defensive mechanisms, such as lymphocyte recirculation and particles uptake into the lymph nodes can benefit from insulin treatment, whereas glycemic control can benefit transport mechanisms in the lymphatic system, such as lymph flow and lymphatic transport of particles (Poiana, Capatina, 2019:231-236). In a recent clinical trial of T1DM patients, bone biopsy samples were taken which showed the pentosidine content of the trabecular part of the bone was substantially and positively linked to HbA1c and improved in T1DM and fracture patients. Diabetic alterations of blood vessels have been well studied, but much less is known about the lymphatic system, which plays an important role in the transport of particles and defensive responses. Accordingly, we investigated lymphatic changes in diabetic rats. Serum and urine levels of pentosidine can be used as markers for bone strength, as circulating levels of pentosidine are correlated with cortical bone pentosidine. In adults with T2DM, serum pentosidine was associated with an increased risk of vertebral fracture, while urinary pentosidine is correlated with an increased risk of clinical and vertebral fractures (Gursoy, Pöllänen, Könönen, Uitto, 2010:1084-1091).

Conclusion

New research has found that a higher level of urinary pentosidine is significantly associated with an increased incidence of clinical fracture in older patients with T2DM. We also performed a cross-sectional study showing that the serum pentosidine levels in postmenopausal women with T2DM were strongly and positively associated with a prevalent vertebral fracture. Hence, the deposition of pentosidine collagen crosslinks in the bone can be a major cause of

decreased BMD in patients with DM.

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