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Research Progress on the Pathogenesis of Type 2 Diabetes-Related Osteoporosis

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Abstract: *Diabetes is a common chronic disease that can lead to related complications such as osteoporosis. Currently, there is a significant amount of research on the pathogenesis of diabetes-related osteoporosis, focusing on aspects such as high blood sugar, oxidative stress response, changes in cytokines and hormones, etc. The pathogenesis of diabetes is complex and diverse. It is of great significance to have a deeper understanding of its pathogenesis, clarify the relationship between diabetes and osteoporosis, and prevent and treat this disease. This article reviews the latest research findings on the pathogenesis of type 2 diabetes-related osteoporosis at home and abroad, aiming to provide reference for subsequent research and clinical practice.*

Keywords: *Type 2 diabetes; Osteoporosis; Pathogenesis*

1. Introduction

In China, the socioeconomic status is continuously advancing at a rapid pace, with an improvement in residents' living standards. However, the incidence of diabetes is showing an increasing trend year by year, with a younger population being affected. Diabetes is the only major non-communicable disease that increases the risk of premature death. Type 2 diabetes mellitus (T2DM) is the most common type of diabetes, and China has the highest prevalence of diabetes[1]. According to the World Health Organization, the number of people with diabetes increased from 108 million in 1980 to 422 million in 2014. In 2019, approximately 463 million adults had diabetes, leading to 4.2 million deaths. The number of diabetes patients is rapidly growing, and it is estimated that by 2045, there will be 700 million patients.

Complications of diabetes affect the kidneys, retina, cardiovascular system, neurons, liver, and bones, with diabetic osteoporosis (DOP) being one of them[2]. Osteoporosis is characterized by low bone mass and degeneration of bone microstructure, leading to increased bone fragility and a higher risk of fractures[3]. Diabetes and its complications impose a significant economic burden on patients, their families, society, and the country. Currently, the pathogenesis of diabetic osteoporosis is not fully understood, possibly related to high blood sugar levels, oxidative stress response, changes in cytokines and hormones, among other factors. This article reviews and summarizes the research progress both domestically and internationally, providing an overview of the pathogenesis of diabetic osteoporosis to serve as a reference for future studies.

2. The pathogenesis of type 2 diabetes-related osteoporosis

2.1 High blood sugar

High blood sugar levels can have adverse effects on bone health. Research indicates that high concentrations of glucose can reduce bone mineral quality by affecting osteoblasts and the mineralization process they induce[4]. High blood sugar induces oxidative damage, disrupts bone metabolism balance, and leads to bone loss[5]. Elevated blood sugar levels can increase the production of advanced glycation end products (AGEs), promoting the occurrence of osteoporosis. AGEs can induce apoptosis in bone cells, disrupting bone homeostasis[6]. Studies have shown that AGEs can impair bone cell function by reducing osteoblasts and increasing osteoclast activity, severely disrupting bone homeostasis. High blood sugar has been found to have toxic effects on the differentiation of bone

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marrow mesenchymal stem cells (MSCs), shifting from fat production to bone formation. AGEs accumulated with age significantly reduce bone density. Further research confirms that AGEs play a crucial role in inducing inflammation and bone loss in the pathogenesis of osteoporosis, particularly in impaired bone formation[7]. Clinical findings show that diabetic patients have significantly higher serum AGE levels than non-diabetic individuals. With age, AGEs accumulate in various tissues, including atherosclerotic plaques in coronary arteries, kidneys, brain, and bones[8]. The transcription factor FOXO1 plays a key role in AGE-induced bone cell dysfunction and apoptosis by regulating cysteine protease-3, sclerostin, and RANKL. Moreover, high blood sugar levels can also interfere with the mineralization of mature osteoblasts and the function of fully differentiated extramedullary adipocytes[9]. Osteoblasts exposed to high glucose levels exhibit reduced proliferation capacity, slow extracellular matrix synthesis, and subsequently slow maturation and mineralization. Therefore, a high blood sugar environment is detrimental to bone formation and maintenance[10].

2.2 Oxidative stress response

Oxidative stress (OS) is an important factor leading to aging and disease, characterized by excessive production or insufficient degradation of reactive oxygen species (ROS) under pathological conditions[11]. ROS are mainly generated through three pathways: mitochondria, xanthine oxidase, and NADPH oxidase. The primary mechanism by which ROS affect bone metabolism is by promoting apoptosis and inhibiting differentiation of osteoblasts, while increasing osteoclast formation. ROS reduce the expression of Runx2 and ALP during the osteogenic differentiation of bone marrow mesenchymal stem cells. The formation of collagen I and BMP2 is also inhibited by ROS, thereby weakening bone mineralization.Furthermore, ROS induce mitochondrial apoptosis in osteoblasts[12]. Elevated levels of ROS can increase the expression of pro-inflammatory cytokines[13]. Oxidative stress provides a new perspective for the treatment of postmenopausal osteoporosis. Some nutrients with strong antioxidant properties are beneficial for the treatment of postmenopausal osteoporosis[14]. Increasing evidence suggests a close relationship between ROS and osteoclast formation. ROS can interact synergistically with osteoclasts. ROS produced by osteoclasts regulate bone homeostasis by stimulating and promoting bone tissue resorption[15]. Studies have shown that ROS play a mediatory role in osteoclast differentiation induced by RANKL, such as controlling the movement of the crucial osteoclast transcription factor NF-κB. ROS can regulate NF-κB activation by inhibiting the phosphorylation of IκBα. Another key osteoclast transcription factor, NFATc1, is also associated with ROS activity[16].

2.3 Cell Cytokines and Hormonal Changes

2.3.1 Increase in Inflammatory Cytokines

High glucose stimulation can promote the production of pro-inflammatory cytokines and chemokines in osteoblasts of Type 2 Diabetes Mellitus (T2DM) fracture patients. In the presence of TNF-α and high glucose, the viability of the osteoblast-like MG-63 cells in vitro is reduced, leading to apoptosis[10]. TNF-α effectively promotes bone resorption by stimulating the proliferation and differentiation of osteoclast precursor cells in the bone marrow into mature osteoclasts, accelerating the process of bone resorption[17]. By inhibiting the expression of interleukin-6 (IL-6), which promotes osteoclast generation, activation of Nrf2 in osteoblasts can directly inhibit osteoclast formation. Nrf2 exhibits a dual inhibitory effect by directly acting on osteoclasts and indirectly supporting osteoclast-supporting cells[18]. By negatively regulating cell differentiation through the inhibition of Runx2-dependent transcriptional activity in osteoblasts[19], Nrf2 can lead to diabetic osteoporosis.

2.3.2 Reduction in Insulin-like Growth Factor-1 (IGF-1)

Insulin can stimulate cell DNA synthesis, induce cell proliferation, and promote the synthesis of bone sialoprotein and collagen. Due to its structural similarity to insulin, Insulin-like Growth Factor-1 (IGF-1) is mainly secreted by liver cells, acts on osteoblasts, and plays a role in promoting synthetic metabolism. It accelerates collagen synthesis and bone matrix mineralization to promote bone formation. Serum IGF-1 levels in patients with Type 2 Diabetes Mellitus (T2DM) are positively correlated with Bone Mineral Density (BMD), and a decrease in IGF-1 levels is a risk factor for fractures in patients[20]. IGF-1 plays a crucial regulatory role in the skeleton, enhancing bone matrix deposition, reducing collagen degradation, and enhancing osteoblast recruitment[21]. Individuals with osteoporosis have a 40% lower bone marrow concentration of IGF-1 compared to those without osteoporosis. Therefore, it has important predictive value as a standard for osteoporosis and risk of

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fragility fractures[22]. In addition, IGF-1 can at least partially promote the proliferation and differentiation of bone marrow mesenchymal stem cells through the Wnt/β-catenin pathway[23]. IGF-1R has a direct effect on chondrocytes, as increased apoptosis and decreased proliferation were observed in mouse chondrocytes after knocking out the IGF-1R gene[24]. Studies have shown that both osteoblasts and osteoclasts have insulin receptors on their surface, and insulin signaling can regulate bone formation in osteoblasts and bone resorption in osteoclasts. The higher the insulin resistance in female T2DM patients, the greater the risk of osteoporosis. Furthermore, with increasing insulin resistance, other related factors such as pro-inflammatory cytokines also increase, adversely affecting bone health beyond the synthetic metabolic effects of insulin on bones, leading to decreased bone density[25].

2.3.3 Changes in Adipokine Levels

Adipokines mainly include leptin, cytokines (such as chemerin), and adiponectin. Leptin can influence bone resorption and directly promote the differentiation of osteoblasts[26]. It stimulates osteoclast production by inducing NF-κB receptor activation ligands through Th17 and promotes bone erosion[27]. Leptin has been shown to regulate bone mass by enhancing the sympathetic nervous system in the hypothalamus through leptin receptors and interfering with bone formation through adrenergic receptors in osteoblasts. Leptin also increases bone resorption by upregulating RANKL expression in osteoblasts, stimulating osteoclast activity[28]. Recent studies have shown that leptin has beneficial effects on bone synthesis as it can alter the differentiation of bone marrow mesenchymal stem cells into osteoblasts. Additionally, leptin can stimulate the central nervous system and neuroendocrine system to release corresponding mediators, indirectly affecting bone metabolism. In rats with osteoporosis, leptin and melatonin can enhance the microstructure of bone trabeculae, promote bone growth, reduce trabecular damage, and repair bone tissue. The combination effect is even more potent[29]. Cytokines, as a type of adipocyte-derived signaling molecule, can promote adipocyte differentiation. Disruption of the chemerin and its receptor CMKLR1 signal not only blocks fat generation in cells but also promotes osteoblast generation[30]. The expression of chemerin in bone tissue is positively correlated with osteogenic genes. Knockout mice lacking chemerin receptors CMKLR1 and GPR1 show reduced bone mass and osteoblast differentiation, indicating that chemerin signaling plays a significant role in regulating bone formation in the body[31]. Adiponectin shows a significant negative correlation with bone density[32]. Adiponectin, with a protein structure, is a hormone synthesized by adipocytes. Studies have found a close relationship between adiponectin and the onset of Type 2 Diabetes Mellitus. Additionally, adiponectin is involved in the regulation of bone metabolism, affecting the activity of osteoclasts and osteoblasts[33]. Postmenopausal women with Type 2 Diabetes Mellitus-related osteoporosis have significantly higher serum adiponectin concentrations compared to healthy individuals. Serum adiponectin levels are an independent risk factor for decreased Bone Mineral Density (BMD) in different weight groups. Therefore, its levels may help predict osteoporotic fractures, thus achieving optimal osteoporosis prediction. However, this study is cross-sectional and cannot explore the long-term effects of adiponectin on bone remodeling and bone density[34].

2.3.4 Decreased Levels of Sex Hormones

Sex hormones play a crucial role in bone metabolism, with both testosterone and estrogen playing key roles in maintaining bone mass. Estrogen is an important regulatory factor in bone metabolism, exerting bone-protective effects by reducing bone resorption and maintaining bone formation. The lack of estrogen enhances osteoclast bone resorption due to increased osteoclast numbers and activity, as well as increased osteoblast apoptosis. Therefore, estrogen deficiency in postmenopausal women can lead to osteoporosis[10]. The absence of estrogen and aging not only directly affect changes in bone mass but also induce various pathophysiological changes, such as the secretion of inflammatory factors and activation of hypoxia-inducible factors, which can indirectly interfere with the bone remodeling process[12]. Compared to healthy women, women with Type 2 Diabetes Mellitus have lower bone density and lower trabecular bone scores. Therefore, the coexistence of estrogen deficiency and diabetes may further exacerbate bone loss[35]. There is an interaction between estrogen and follicle-stimulating hormone (FSH), with low estrogen and high FSH levels associated with a higher prevalence of osteoporosis. In most clinical studies, estrogen and FSH levels in T2DM patients are lower than in non-diabetic patients. In women, FSH is negatively correlated with Bone Mineral Density (BMD) at three sites, and FSH levels are positively correlated with osteoporosis in women, while estrogen levels in T2DM patients are negatively correlated with osteoporosis[36].

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2.4 Chronic Complications of Diabetes

Type 2 Diabetes Mellitus-related osteoporosis can cause complications in organs such as the kidneys and liver, leading to an imbalance between bone resorption and formation, thereby accelerating the progression of osteoporosis. Clinically, patients with diabetic nephropathy often develop concurrent osteoporosis, characterized by persistently elevated blood sugar, glycosylated hemoglobin, significant proteinuria, increased water intake and urine output, and decreased bone density[37]. Patients with Type 2 Diabetes Mellitus have a high risk of peripheral vascular diseases, including carotid artery stenosis and peripheral arterial disease in the lower limbs. Microvascular disease mediates microstructural changes by increasing cortical porosity and is associated with reduced bone turnover[38]. This was discovered in a post-analysis of 933 patients with Type 2 Diabetes Mellitus. A significant correlation between arterial calcification and osteoporosis is observed only in women, with a higher prevalence of osteoporosis in women with calcification compared to those without calcification. Women with calcification have lower bone density in the hip joint and femoral neck, indicating a link between the vascular system and osteoporosis. This study demonstrates a positive correlation between lower limb arterial calcification and osteoporosis in postmenopausal women with Type 2 Diabetes Mellitus. Female patients with lower limb arterial calcification should actively undergo lower limb artery examinations to be vigilant about the risk of osteoporosis[39]. In addition, elderly patients with Type 2 Diabetes Mellitus have a significantly higher incidence of microvascular and macrovascular complications compared to the middle-aged group. The prevalence of hypertension and osteoporosis is also higher in the elderly group than in the middle-aged and younger groups[40]. Diabetes microvascular disease, as one of the diabetes-specific complications, can lead to bone loss and increased bone fragility [41], thereby increasing the likelihood of developing osteoporosis.

2.5 Body Mass Index (BMI)

Obesity refers to a condition characterized by excessive accumulation of body fat, especially triglycerides, resulting from the interaction of various factors such as social, behavioral, psychological, and metabolic factors. Obesity is associated with many adverse consequences, such as hypertension, diabetes, cancer, and osteoporosis[12]. Many researchers have conducted extensive studies on the relationship between BMI and osteoporosis. In elderly patients with osteoarthritis, especially women with lower BMI values, bone density levels are often lower[42]. Studies have shown that a high BMI has a protective effect against osteoporosis and fractures in men and postmenopausal women[43]. Based on a nationwide cross-sectional study in Korea, a BMI of 23.0 to 24.9 kg/m² was found to be the optimal range for reducing the risk of osteoporosis and Type 2 Diabetes Mellitus in Korean men over the age of 50 and postmenopausal women[44]. Due to the similarity of the study population to the physical constitution of Chinese residents, this study has higher reference value compared to studies in Europe and America. Excessive accumulation of fat can lead to a series of metabolic abnormalities and diseases, including insulin resistance, atherogenic dyslipidemia, non-alcoholic fatty liver disease, β-cell dysfunction, and Type 2 Diabetes Mellitus. Obesity, especially abdominal and visceral fat distribution-related obesity with increased intrahepatic and intramuscular triglyceride content, is a major risk factor for prediabetes and Type 2 Diabetes Mellitus because it leads to insulin resistance and β-cell dysfunction. The global increase in obesity prevalence has correspondingly increased the prevalence of Type 2 Diabetes Mellitus. Understanding the mechanisms by which excess body fat adversely affects factors related to the pathogenesis of Type 2 Diabetes Mellitus can provide new therapeutic interventions for preventing and treating this debilitating disease[45]. Although weight loss is the most important factor in reducing the risk of developing diabetes, research has also found that even without weight loss, achieving the goal of at least 150 minutes of physical activity per week can reduce the incidence of Type 2 Diabetes Mellitus by 44%[46]. Fat accumulation in the obese group can increase bone fragility and induce osteoporosis[47]. Studies have shown that bone density increases with increasing BMI, as higher BMI can increase the load-bearing capacity of bones and promote bone formation[48].

2.6 Other Factors

Genetic factors play a crucial role in the development of Type 2 Diabetes Mellitus, while unhealthy dietary habits and sedentary lifestyles are also strong contributors to Type 2 Diabetes Mellitus[2]. Research has shown a close relationship between vitamin D and the incidence of diabetes. Vitamin D, a fat-soluble vitamin, plays a vital role in regulating calcium homeostasis in bone metabolism and muscle function. 25-hydroxyvitamin D (25OHD) is a metabolite considered the best indicator of vitamin D status[49]. The primary physiological function of vitamin D is to maintain normal levels of calcium and phosphorus in the body. Vitamin D deficiency can lead to secondary hyperparathyroidism and

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subsequent bone loss, resulting in osteoporosis and fractures, as well as mineralization defects leading to long-term osteomalacia. It can also cause muscle weakness, increasing the risk of falls and fractures. In the osteoporosis (OP) population, there is a negative correlation between serum 25-hydroxyvitamin D (25(OH)D) and fasting blood glucose (FBG). It is recommended that OP patients supplement with vitamin D, as this can not only improve bone quality in OP patients but also elevate their blood sugar levels. Future prospective intervention studies with larger sample sizes are needed to confirm this hypothesis[50]. Supplementation with vitamin D and calcium can treat nutritional rickets and moderately reduce the risk of severe fractures in elderly individuals with poor vitamin D status or low calcium intake. In conclusion, research results indicate that supplementing with vitamin D alone does not have a beneficial effect on the risk of fractures in vitamin D-rich adults. However, in elderly individuals, especially those with low vitamin D levels and low calcium intake, combined supplementation of calcium and vitamin D may reduce the risk of hip fractures and other major fractures by approximately 20%[51].

In patients with Type 2 Diabetes Mellitus (T2DM), insulin function gradually decreases with the progression of the disease. Prolonged insulin deficiency can lead to persistent hyperglycemia and reduced bone turnover, affecting osteoclast activity and promoting bone resorption[52]. Mitochondrial ferritin (FtMt) is a protein that stores iron ions and intercepts toxic iron ions in cell mitochondria. Iron dropletting is an iron-dependent form of cell damage that may be related to the pathogenesis of T2DM osteoporosis (T2DOP). Iron-deficiency anemia has been found in the bones of T2DOP rats. Overexpression of FtMt under high-sugar conditions reduces iron-deficiency anemia in osteoblasts, and FtMt deficiency-induced mitochondrial autophagy may be involved in the pathogenesis of T2DOP. This suggests that FtMt may be a potential target for the treatment of T2DOP. Iron homeostasis imbalance and osteoblast iron deficiency may be mechanisms of T2DOP [50].

Research has shown that combined aerobic and resistance exercise is highly effective for Type 2 Diabetes Mellitus (T2DM) patients in improving muscle strength and fatigue, blood sugar control, and health-related quality of life. This indicates the importance of better clinical care for T2DM patients engaging in both aerobic and resistance exercises. Exercise rehabilitation therapy can significantly enhance the quality of life for patients with Type 2 Diabetes Mellitus-related osteoporosis, improve symptoms of Type 2 Diabetes Mellitus-related osteoporosis, and thereby prevent fractures. This approach may be an effective non-surgical treatment for Type 2 Diabetes Mellitus-related osteoporosis [53]. Postmenopausal women with osteoporosis can slow the increase of bone resorption markers by supplementing with vitamin E, and CTX may prevent bone loss through its anti-resorptive activity [54].

3. Conclusion

In summary, due to the complex and diverse pathogenesis of Type 2 Diabetes Mellitus-related osteoporosis, the process of bone loss is often subtle and does not directly cause noticeable symptoms until local bone strength cannot bear the load, leading to pain and bone deformities. Additionally, the weak awareness of preventing bone loss and limitations in bone mass measurement methods result in osteoporosis being systematically treated only when severe complications arise, placing a heavy burden on patients and healthcare resources. The signaling pathways and driving genes involved in the bone injury process are not fully understood. Further research is needed to elucidate the molecular mechanisms of diabetic bone disease. Therefore, identifying common pathophysiological changes in various high-risk populations and implementing targeted interventions can slow down the progression of bone loss and reduce the incidence of osteoporosis. Developing new treatment strategies for diabetic bone disease patients is of great importance. Furthermore, the diagnostic criteria for diabetic bone disease in patients of different ages and disease courses are not yet clear and require further investigation.

Therefore, early intervention and treatment of high-risk populations for osteoporosis are crucial in preventing bone loss. The level of awareness among patients regarding Type 2 Diabetes Mellitus-related osteoporosis still needs to be raised. Therefore, it is of great importance to clarify the pathogenesis of Type 2 Diabetes Mellitus-related osteoporosis and elucidate the relationship between Type 2 Diabetes Mellitus and osteoporosis. This article mainly summarizes the current research progress on Type 2 Diabetes Mellitus-related osteoporosis at home and abroad, aiming to provide a reference for future studies.

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