ENDOCRINOLOGY RESEARCH AND PRACTICE

SOCIETY OF ENDOCRINOLOGY AND METABOLISM OF TÜRKİYE

Diabetic Osteodystrophy

REVIEW
Endocrinol Res Pract. 2024;28(3):175-180

ABSTRACT

Diabetes mellitus (DM) is associated with an increased risk of fractures due to deterioration of bone quality, which can be referred to as "diabetic osteodystrophy." Furthermore, the risk of fracture is increased in DM, even if bone mineral density is normal or high and is associated with increased morbidity if a fracture develops. In addition to the pathophysiological mechanisms of DM, diabetes-related complications and drugs used in the treatment of DM may also affect bone health. Moreover, the increased risk of falling due to microvascular complications, hypoglycemia, and postural hypotension also contributes to the development of fractures. Individuals with DM should be screened for osteoporosis with recommendations similar to those of the general population. When diagnosing osteoporosis and deciding on treatment, it should be kept in mind that DM may be an important risk factor, and lower threshold values of the T score should be used.

Keywords: Diabetes mellitus, fracture risk, osteodystrophy, osteoporosis

Introduction

Diabetes mellitus (DM) is a common metabolic disease that affects millions of people, and its frequency is rapidly increasing worldwide due to the increase in obesity, sedentary lifestyle, and aging population.[1] In recent years, it has been understood that DM significantly affects bone health and that both type 1 and type 2 DM are associated with increased fragility and fracture risk.[2,3] Osteoporosis is a systemic metabolic disease characterized by increased bone fragility and fracture risk.[4] In fact, osteoporosis is another disease that is increasing worldwide due to the aging population and is an alarming problem for public health due to the severe morbidity and mortality caused by fractures.[5]

Currently, deterioration of bone quality and increased risk of fractures are defined as one of the complications of diabetes.[3,6] In diabetic individuals, the risk of fractures is increased compared to the general population, and fractures may occur at earlier ages.[7] Moreover, the risk of fracture is increased in diabetic individuals with normal or even increased bone mineral density (BMD), and the presence of DM is associated with increased morbidity in individuals who develop fractures.[8,9]

Bone health may be affected by the pathophysiological mechanisms of DM, the presence of diabetes-related complications, and the drugs used to treat DM (Table 1). This article will systematically examine the effects of DM on bone health and the increased fracture risk associated with DM.

Pathophysiological Mechanisms and Bone in Diabetes Mellitus

Inflammation

The presence of DM causes a chronic low-grade inflammatory state, and this chronic inflammatory process activates osteoclastogenesis.[10] Tumour necrosis factor alpha (TNF-α), a product of increased inflammation, has been shown to increase the number of osteoclasts in diabetic mice.[11] It has also been shown that increased TNF-α levels in DM are associated with a high receptor activator of nuclear factor kappa B ligand (RANKL)/ osteoprotegerin (OPG) ratio, which indicates a decrease in osteoblast formation and function.[12]

Formation of Advanced Glycation End Products

It has been shown that advanced glycation end products (AGEs) resulting from hyperglycemia accumulate excessively in bones. Advanced glycation end products disrupt osteoblast development, function, and the adhesion of osteoblasts to the collagen matrix.[13] It has been shown that type 1 collagen and osteocalcin synthesis in human osteoblast cells

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Received: April 6, 2024
Revision Requested: May 13, 2024
Last Revision Received: May 24, 2024
Accepted: June 3, 2024
Publication Date: July 3, 2024

Cite this article as: Eren MA, Öz Gül Ö. Diabetic osteodystrophy. *Endocrinol Res Pract.* 2024;28(3):175-180.

DOI: 10.5152/erp.2024.24463

Table 1. Factors that Affect Bone Health in Diabetes Mellitus

Pathophysiological mechanism	• Inflammation • Formation of AGEs • Insulin deficiency/insulin resistance • Hyperglycemia itself • Adiposity of bone marrow
Complications	• Diabetic retinopathy • Diabetic neuropathy • Diabetic nephropathy
Some antidiabetic drugs	• Thiazolidinediones • Sulfonylureas (increase fracture risk) • SGLT-2 inhibitors (especially canagliflozin)

AGEs, advanced glycation end products; SGLT-2, sodium–glucose co-transporter 2.

and parathormone synthesis in parathyroid cells are inhibited by AGEs in vitro.[14] On the other hand, the increase of AGEs in collagen fibers in a non-enzymatic cross-linked manner also causes physical deterioration in bone strength.[15] In addition, AGEs mediate the formation of reactive oxygen species, leading to vascular inflammation and microangiopathy, which in turn leads to impaired bone remodeling.[16]

Effects of Insulin on Bone Tissue

The insulin receptor is found on the surface of both osteoblasts and osteoclasts. Physiological insulin concentrations increase osteoblast proliferation rate, collagen synthesis, and alkaline phosphatase production and inhibit osteoclast activity.[17] In insulin deficiency, mineral binding rate and mineralized surface area, osteoid volume, osteoblast activity, and number were decreased.[17] It has been shown that bone turnover also decreases even in insulin-resistant cases with high insulin levels.[18]

In observational studies, insulin therapy has been associated with an increased risk of fractures in patients with type 2 DM.[19-20] It should not be forgotten that insulin is used in people with high DM duration and microvascular complications, especially renal failure. The risk of fracture may also increase due to hypoglycemia-related falls rather than insulin itself.[21]

Effects of Hyperglycemia Itself

Hyperglycemia itself can also affect bone metabolism. First, high blood glucose levels can result in hypercalciuria. In some studies, hyperglycemia causes functional hypoparathyroidism, resulting in a decrease in active vitamin D.[22] This functional change in vitamin D may lead to a decrease in calcium reabsorption from the urine and calcium absorption from the intestine.[23] In addition, hyperglycemia has negative effects directly on osteocalcin—one of the very few proteins specific to osteoblasts—and, therefore, on bone turnover.[23]

Effects on Bone Marrow

Obesity accompanying type 2 DM causes increased adiposity in the bone marrow, as in other parts of the body, leading to cellular hypermetabolism, depletion of stem cells, accumulation of senescent cells, and inflammation. This situation causes a decrease in factors secreted by bone marrow adipocytes and suppression of normal tissues due to the space-occupying effect of fat tissue. As a result, the production of osteoblastic or hematopoietic cells, which are necessary for normal skeletal homeostasis, is impaired .[18]

Complications of Diabetes Mellitus and Bone

Diabetic Retinopathy

Diabetic retinopathy is the most common microvascular complication of DM, affecting almost 1 in every 3 diabetics.[24] Ivers et al[25] found that the presence of diabetic retinopathy was associated with an increased risk of fracture. Lim et al[26] showed that the presence of diabetic retinopathy was associated with decreased BMD and, therefore, increased prevalence of osteoporosis in diabetic women, but not in men. Additionally, many studies show changes in blood–bone turnover markers, which indicate that bone metabolism is impaired in the presence of retinopathy in individuals with type 2 DM.[27-30]

Diabetic Neuropathy

Diabetic neuropathy is a common microvascular complication of diabetes and is associated with an increased risk of falls and fractures due to decreased peripheral sensation, impaired motor coordination, and postural hypotension.[31] Kim et al[32] showed that the presence of diabetic peripheral neuropathy was an independent risk factor for fractures in individuals with type 2 DM. Some studies are showing that the presence of neuropathy is associated with decreased BMD in individuals with both type 1 and type 2 DM.[33-35] However, other studies showed that diabetic neuropathy does not have a negative effect on bone.[36]

Diabetic Nephropathy

Diabetic nephropathy, one of the common microvascular complications of diabetes, is detected by microalbuminuria in the early stages and may progress to loss of renal function and end-stage renal failure over time.[37] The kidney is an important organ that regulates bone homeostasis, and renal failure may disrupt bone metabolism and lead to the development of renal osteodystrophy.[38] While deterioration of bone metabolism is expected in patients with renal failure due to diabetes, bone tissue may be affected without loss of function. Han et al[39] showed that BMD decreases and bone metabolism markers deteriorate in relation to the level of albuminuria in the early diabetic nephropathy stage detected with microalbuminuria. Ye et al[40] found that the risk of hip fracture increased as the glomerular filtration rate (GFR) level decreased in individuals with type 2 DM without known chronic kidney disease. Zhao et al[41] showed that there was an increase in bone turnover in the early stage of diabetic nephropathy without any change in BMD.

MAIN POINTS

- Bone mineral deficiency and increased fracture risk due to diabetes can be considered complications of diabetes mellitus.
- Diabetes itself, its complications, and the agents used to treat diabetes can negatively affect bone tissue.
- In the presence of diabetes mellitus, especially type 2 diabetes, having normal bone mineral density does not always exclude the risk of fracture.
- Agents for the treatment of diabetes should be selected carefully to avoid increasing the risk of fractures in certain patient groups.
- Treatment decisions for osteoporosis in the presence of diabetes may differ from those in the normal population.

Antidiabetic drugs and bone

Since the risk of fracture is high in patients with diabetes, it is essential to understand the effect of antidiabetic drugs used in the treatment of bone.

Metformin

Metformin, used as the first line, is the most prescribed antidiabetic agent. In preclinical studies, they have been shown to prevent osteoblast apoptosis and increase bone mass and strength by reducing AGE accumulation and ROS formation.[6] Although there are clinical studies showing a slight increase in BMD with metformin use, it is thought to be beneficial or neutral on the fracture risk.[42,21] It can also be used as the first choice in diabetic patients with osteoporosis.[21]

Sulfonylureas

Sulfonylureas increase osteoblast proliferation and differentiation.[43,44] In clinical studies, it has been shown to be beneficial or at least neutral for bone health.[21,45] However, in those over 65 years of age or at high risk of hypoglycemia, the risk of hip fracture increases due to the increased risk of falling, and they should be used with caution in this group.[46]

Incretin-Based Agents

Incretin hormones can stimulate osteoblastogenesis by acting directly on osteoblasts and indirectly by increasing insulin. Additionally, incretin hormones can inhibit osteoclastogenesis by stimulating calcitonin production.[45] While there are studies of dipeptidyl peptidase 4 (DPP-4) inhibitors showing a significant reduction in the risk of fractures, there are also studies showing that they have no effect on bone.[47-50] Data indicate that glucagon-like peptide 1 (GLP-1) analogues are not associated with an increase in fracture risk; moreover, they reduce the risk of fracture.[51,52] Therefore, it can be said that both groups of drugs have a beneficial or at least neutral effect in terms of bone health.[53]

Thiazolidinediones

Thiazolidinediones (TZDs) increase insulin sensitivity by acting as peroxisome proliferator-activated receptor gamma (PPAR-γ) agonists.[54] Thiazolidinediones affect various transcription factors through PPAR-γ, causing mesenchymal stem cells to differentiate into adipocytes rather than osteoblasts; thus, adipogenesis is stimulated, and osteoblastogenesis is suppressed.[55,56] Additionally, in this way, bone marrow fat increases and osteoclast differentiation is encouraged.[55,56] It has been shown that TZD use increases the risk of fractures in the hip, spine, and peripheral regions, especially in women, and the risk continues in the year after the drug is discontinued.[21,57] There are also data showing that the risk of osteoporosis increases 1 year after TZD use begins and when the total duration exceeds 2 years.[57] For this reason, the use of TZDs should be avoided, especially in postmenopausal women with osteoporosis or in individuals at high risk for osteoporosis.[53]

Sodium–Glucose Co-Transporter 2 Inhibitors

Sodium–glucose co-transporter 2 inhibitors increase urinary glucose and sodium excretion by lowering the renal glucose threshold. They are also known to have a cardio-renal protective effect.[58] There is no SGLT-2 receptor in bone. Therefore, these drugs have an indirect effect on bone metabolism. Sodium–glucose co-transporter 2 inhibitors lead to an increase in urinary calcium excretion and renal phosphorus reabsorption. These electrolyte changes lead to secondary hyperparathyroidism and an increase in fibroblast growth factor 23. Although these 2 hormones have opposite effects on the formation of active vitamin D, the net effect is a decrease in the synthesis of 1, 25-dihydroxy vitamin D. Additionally, it has been reported that there may be an increase in the risk of fracture due to hypotension caused by decreased volume and increased hypoglycemia due to concomitant antidiabetics.[59,60] Despite all these pathophysiological mechanisms, the effect of SGLT-2 inhibitors on bone fracture is controversial, and in general, no clear relationship has been demonstrated that the use of SGLT-2 inhibitors increases the risk of bone fracture. Since some studies have shown negative effects on bone, canagliflozin should be used after careful evaluation of the individual's skeletal risk.[59-61]

Effect of Diabetes Mellitus on Bone Mineral Density and Fracture Risk

It has been reported that BMD measured from the femur and lumbar vertebra is significantly lower in type 1 DM.[62] Although there are conflicting results regarding type 2 DM, large-scale studies have shown that BMD values are significantly higher than in the non-diabetic population.[63,64] Despite this, the risk of fracture in most parts of the skeleton increases in individuals with type 2 DM, as it does in individuals with type 1 DM. A meta-analysis showed that individuals with type 1 DM have a higher risk of hip fracture than individuals with type 2 DM.[63] The risk of hip, pelvis, upper leg, foot, and vertebral fractures is significantly higher in women with type 2 DM.[65] In addition, the presence of DM is a negative prognostic factor for post-fracture mortality in patients with hip fractures.[66]

The increased risk of fractures in individuals with type 2 DM despite high BMD levels can be explained by the increased risk of falling. The risk of falling occurs due to impaired proprioception from peripheral neuropathy, visual impairment from diabetic retinopathy, accommodation changes in the eyes due to rapid fluctuations in glycemia, dizziness, and balance disorders from hypoglycemia, hyperglycemia, or postural hypotension.[67]

Evaluation of the Patient with Diabetes Mellitus in Terms of Osteoporosis

Similar recommendations for the general population are offered for the evaluation of individuals with DM in terms of osteoporosis. In individuals with DM, osteoporosis treatment can be started if there is a fracture in the hip or vertebral region or more than 1 fracture of another region. Bone mineral density measurement with dual x-ray absorptiometry (DXA) is recommended for patients with clinical risk factors.[68] In the presence of DM, unlike the general population, osteoporosis treatment is recommended if the T score is <−2.0, and calculation of the FRAX score is recommended if osteopenia (T score between −1.0 and −2.0) is detected.[68] Diabetes mellitus is not yet included as a risk factor in the FRAX tool. To eliminate this handicap, the following actions can be taken: adding 10 years to the patient's age in the FRAX tool, selecting "Yes" in the "rheumatoid arthritis" section, writing the T value of BMD 0.5 points lower, or combining the Fracture Risk Assessment Tool (FRAX) score with the trabecular bone score value.[7,69-71] Trabecular bone score is a texture index derived from DXA scans of the lumbar spine that evaluates pixel gray level changes and provides an indirect measurement of bone microarchitecture. Trabecular bone score appears to be more accurate than BMD of the lumbar spine for predicting fracture risk in diabetic bone disease, especially in postmenopausal women with T2DM.[71,72] Each of

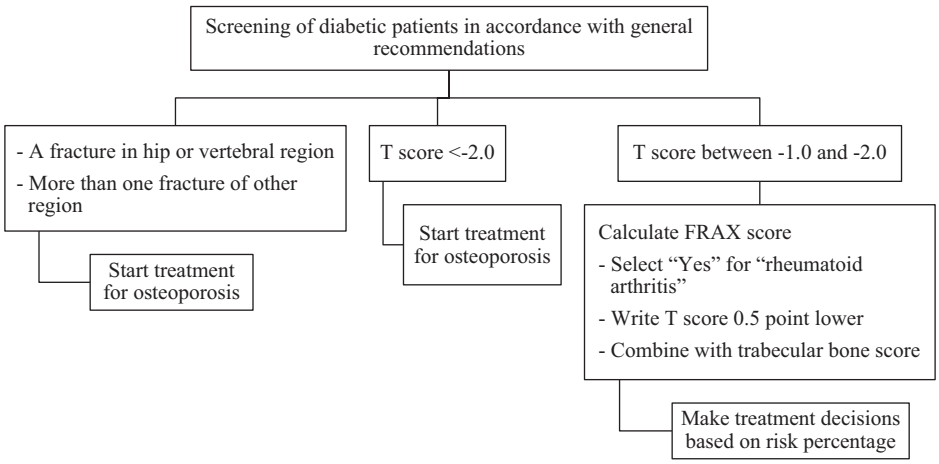

Figure 1. Diagnosis and treatment of osteoporosis in diabetes mellitus.

the proposed FRAX adaptation methods has been shown to improve the performance of the program, but no single method was optimal in all cases with type 2 DM.[70] Diagnosis and treatment of osteoporosis in diabetes mellitus are summarized in Figure 1. Bone mineral density measurements should be repeated every 2-3 years for individuals with diabetes who have a low FRAX score and are not receiving treatment.[68]

Conclusion

Due to the effect of hyperglycemia and some hyperglycemia-related events, bone quality deteriorates, and the risk of fracture increases in the presence of DM. In addition, some of the drugs used in the treatment of DM have negative effects on bone. Moreover, measuring BMD may not always predict the risk of fracture, especially in individuals with type 2 DM. Therefore, when evaluating individuals with DM, protecting bone health should be a part of diabetic care, keeping in mind that the risk of fractures and falls may be higher than in individuals with similar characteristics without diabetes.

Peer-review: Externally peer reviewed.

Author Contributions: Concept – M.A.E.; Design – M.A.E., Ö.Ö.G.; Supervision – Ö.Ö.G.; Resources – M.A.E., Ö.Ö.G.; Literature Search – M.A.E.; Writing – M.A.E.; Critical Review – Ö.Ö.G.

Declaration of Interests: M.A.E and Ö.Ö.G have no conflicts of interest to declare.

Funding: This study received no funding.

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