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DIABETES MELLITUS AND BONE HEALTH: CONTEMPORARY CONCEPTS OF ITS ASSOCIATION WITH OSTEOPOROSIS

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Abstract. *Diabetes mellitus (DM) and osteoporosis are chronic diseases with increasing prevalence. Globally, 589 million adults live with DM, while osteoporosis affects approximately 500 million people, including 21.2% of women and 6.3% of men aged over 50 years. These conditions frequently coexist, giving rise to the concept of diabetic osteopathy (DO), which encompasses structural and functional bone abnormalities caused by chronic hyperglycaemia and other diabetes-related metabolic disturbances.The pathophysiology of DO involves chronic hyperglycaemia, oxidative stress, impaired Wnt signalling, accumulation of advanced glycation end-products (AGEs), and insulin deficiency or resistance. Type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM) have distinct skeletal risk profiles. T1DM is associated with reduced bone mineral density (BMD) and increased fracture risk. In T2DM, skeletal integrity may be substantially impaired despite normal or increased BMD, demonstrating that bone quality, rather than bone mass alone, is clinically important. Hip fracture risk is approximately 1.3–1.7-fold higher, indicating that BMD underestimates skeletal fragility in T2DM.T2DM is generally characterised by low bone turnover, impaired bone formation, altered microarchitecture, and poorer material properties, driven by hormonal abnormalities, inflammation, vascular complications, and disrupted cellular signalling. Fractures are associated with delayed recovery, more complications, and increased mortality. Glucose-lowering therapies may also modify skeletal health. Metformin, dipeptidyl peptidase-4 inhibitors, and glucagon-like peptide-1 receptor agonists generally have neutral or potentially beneficial skeletal effects. Thiazolidinediones increase fracture risk, whereas sulfonylureas and insulin may increase fractures partly through hypoglycaemia-related falls. The fracture signal observed with canagliflozin in CANVAS was not confirmed in CREDENCE or pooled analyses. Consequently, fracture-risk assessment and evaluation of bone health should be integrated into routine diabetes care.*

Keywords: *Diabetes mellitus, osteoporosis, BMD (bone mineral density), fractures, antihyperglycemic agents.*

Introduction

Global burden of diabetes and osteoporosis

Diabetes mellitus and osteoporosis are highly prevalent chronic non-communicable diseases and represent major global public health challenges. According to the *International Diabetes Federation Diabetes Atlas*, 11th edition, published in 2025, an estimated 589 million adults aged 20–79 years were living with diabetes worldwide in 2024. This number is projected to increase to 853 million by 2050, representing an increase of approximately 45% [1].

Osteoporosis also imposes a substantial global health burden. According to estimates reported by the International Osteoporosis Foundation (IOF), approximately 500 million women and men worldwide may be affected. Among individuals aged over 50 years, the estimated prevalence of osteoporosis is 21.2% in women—approximately one in five—and 6.3% in men—approximately one in sixteen. Thus, osteoporosis is estimated to be approximately 3.4 times more prevalent in women than in men. However, within its current global estimate of 500 million affected individuals, the IOF (Intetrnational Osteoporosis Foundation) does not provide separate absolute numbers for women and men; sex differences are primarily expressed through prevalence estimates.

It is important to distinguish the prevalence of osteoporosis from the lifetime risk of osteoporotic fracture. Worldwide, approximately one in three women and one in five men aged over 50 years are expected to sustain an osteoporosis-related fracture during their remaining lifetime. These figures indicate the remaining lifetime risk of osteoporotic fracture and should not be interpreted as the proportion of individuals who currently meet the diagnostic criteria for osteoporosis [2].

As the prevalence of osteoporosis increases markedly with age, rising life expectancy and the rapid ageing of the global population are likely to result in a further increase in the worldwide burden of the disease. Type 2 diabetes (T2D) and osteoporosis share several risk factors, including advanced age, physical inactivity, and adverse lifestyle changes; therefore, they frequently coexist, particularly among older adults [3].

However, the true prevalence of their coexistence is difficult to determine accurately. One reason is that individuals with T2D may have normal or even increased bone mineral density (BMD) despite being at increased risk of fragility fractures. Because of this apparent paradox, conventional diagnostic criteria based on DXA-derived BMD and T-scores, as well as standard risk assessment using the FRAX algorithm, may underestimate the actual fracture risk in individuals with T2D [4,5].

Aim: This review aims to provide an updated overview of the relationship between diabetes mellitus and bone health, with particular emphasis on current concepts linking diabetes to osteoporosis. It also summarizes the potential mechanisms

underlying diabetes-associated bone fragility, as well as contemporary strategies for the prevention and treatment of these conditions.

Methods: A systematic literature search was conducted to identify relevant human studies published in two electronic databases, PubMed and the Cochrane Library, up to June 2026. The available evidence was critically reviewed and synthesized, together with findings from the authors' own research.

Results and discussion

Metabolic Bone Disease and Diabetes: Pathophysiological Mechanisms

Diabetic bone disease, also referred to as diabetic osteopathy, encompasses a complex spectrum of structural and functional skeletal abnormalities resulting from chronic hyperglycaemia and other metabolic disturbances associated with diabetes mellitus. These alterations in bone metabolism may include varying degrees of bone loss, reduced bone mineral density (BMD), impaired bone microarchitecture, compromised bone quality, and increased skeletal fragility.

Individuals with type 1 diabetes (T1DM) have a significantly increased fracture risk compared with individuals without diabetes. The risk is particularly pronounced for hip fractures—approximately fivefold higher—while the risk of non-vertebral fractures is approximately twofold higher. Because reported risk estimates vary among studies and according to fracture site, these values should preferably be presented as approximate estimates [6].

Type 2 diabetes mellitus (T2DM) is associated with chronic low-grade inflammation, driven primarily by hyperglycaemia, insulin resistance, dysfunctional adipose tissue, and obesity-related alterations in adipokine and cytokine secretion. This pro-inflammatory metabolic environment contributes to the development and progression of insulin resistance and adversely affects bone remodelling and bone quality.

Several interrelated mechanisms contribute to skeletal fragility in T2DM. Persistent hyperglycaemia promotes the formation and accumulation of advanced glycation end-products (AGEs) and increases the production of reactive oxygen species (ROS). Non-enzymatic glycation of type I collagen leads to abnormal collagen cross-linking, reduced bone matrix elasticity, and deterioration of the material properties of bone. In addition, the interaction of AGEs with their receptor, RAGE, activates oxidative and inflammatory signalling pathways, further impairing bone-cell function.

Oxidative stress and pro-inflammatory cytokines adversely affect osteoblast differentiation, activity, and survival, thereby reducing bone formation. Although inflammatory signalling may promote osteoclastogenesis and bone resorption under certain conditions, T2DM is frequently characterized by an overall low-turnover skeletal phenotype. Consequently, the increased fracture risk cannot be explained solely by accelerated bone resorption or reduced bone mineral density (BMD).

Instead, it results from a combination of impaired bone formation, abnormal collagen properties, altered cortical and trabecular microarchitecture, accumulation of microdamage, and reduced bone material strength.

These changes help explain the clinical paradox whereby individuals with T2DM may have normal or even elevated BMD but nevertheless experience increased skeletal fragility and fracture risk. Conventional BMD measurements may therefore underestimate diabetes-related deterioration in bone quality. Additional assessment of clinical risk factors and bone microarchitecture, including the trabecular bone score when available, may improve fracture-risk evaluation in this population [7].

Bone metabolisam in diabetes

Diabetes-related skeletal fragility: clinical determinants, pathophysiological mechanisms, and bone characteristics

Skeletal fragility is an increasingly recognized complication of both type 1 diabetes (T1D) and type 2 diabetes (T2D). The increased fracture risk results from a complex interaction between diabetes-related clinical characteristics, direct metabolic effects on bone tissue, deterioration of bone microarchitecture, and an increased propensity to fall. Importantly, conventional bone mineral density (BMD) measurements do not fully capture this risk: BMD is generally reduced in T1D but is often normal or increased in T2D, despite the persistence of clinically relevant skeletal fragility. Thus, diabetes affects not only bone quantity but also bone quality and mechanical competence.

Several clinical features of diabetes are associated with fractures. Insulin therapy, particularly in T2D, has been linked to an increased incidence of fractures, including distal fractures. However, this association should not necessarily be interpreted as a direct adverse skeletal effect of insulin. Rather, insulin treatment may identify individuals with longer disease duration, greater disease severity, and a higher burden of complications. In addition, insulin-associated hypoglycaemia may increase the risk of falls and subsequent fractures. Both microvascular and macrovascular complications contribute to skeletal vulnerability through impaired vision, peripheral and autonomic neuropathy, reduced balance, muscle weakness, altered bone perfusion, and an increased tendency to fall [8, 9].

Glycaemic control also has a complex, non-linear relationship with fracture risk. Chronic hyperglycaemia and higher HbA1c levels are associated with fractures in both T1D and T2D. Conversely, very low HbA1c values—particularly when achieved through intensive glucose-lowering therapy in older individuals with T2D—may be accompanied by an increased risk of hypoglycaemia, falls, and hip fractures. Longer duration of T1D is generally associated with greater fracture risk, whereas T2D may exhibit a biphasic relationship: fracture risk may initially be attenuated by obesity and hyperinsulinaemia but increases with longer disease duration, progressive

accumulation of advanced glycation end-products, vascular complications, and deterioration of bone quality [10].

The pathophysiology of diabetic bone disease is multifactorial. Obesity increases mechanical loading, which may exert an anabolic effect on bone; however, this potentially beneficial effect is counterbalanced by chronic low-grade inflammation, altered adipokine secretion, insulin resistance, and accumulation of visceral and bone marrow adiposity. Although insulin normally stimulates osteoblast activity and bone formation, insulin deficiency in T1D and impaired insulin signalling in T2D may compromise bone formation and skeletal adaptation to mechanical loading [11].

Chronic hyperglycaemia directly impairs osteoblast differentiation and maturation, promotes osteocyte dysfunction and senescence, and may prolong osteoclast survival. It also promotes the formation and accumulation of advanced glycation end-products (AGEs) within the bone matrix. Non-enzymatic glycation disrupts collagen cross-linking, alters matrix mineralization, and reduces the ability of bone to absorb energy, thereby increasing brittleness independently of BMD. Oxidative stress and the accumulation of reactive oxygen species (ROS) further accelerate cellular ageing, impair osteoblast function, and alter angiogenesis and bone microvascular integrity. These metabolic and vascular abnormalities ultimately compromise bone remodelling, material properties, and fracture resistance [12].

Bone turnover is generally reduced in diabetes, particularly in T2D, resulting in the accumulation of older and potentially microdamaged bone. Alterations in bone microarchitecture differ between the two major diabetes types. T1D is predominantly associated with impaired trabecular parameters and reduced bone mass, whereas T2D is more consistently characterized by cortical deficits, particularly increased cortical porosity. These abnormalities may be demonstrated using high-resolution peripheral quantitative computed tomography (HR-pQCT) and help explain why patients with T2D may sustain fragility fractures despite apparently preserved or elevated BMD.

Overall, assessment of skeletal health in diabetes should extend beyond conventional densitometry. Diabetes duration, glycaemic control, insulin therapy, hypoglycaemia, vascular complications, fall risk, bone turnover, and deterioration of bone microarchitecture should all be considered. The discrepancy between BMD and fracture risk supports a diabetes-specific approach to the evaluation of skeletal fragility, integrating both skeletal and extraskeletal determinants of fracture [13].

Type 1 and Type 2 Diabetes: Distinct Risk Profiles for Disorders of Bone Metabolism

Diabetes Risk Factors and Bone Microarchitecture in Adults with Long-standing T1D

Type 1 diabetes is associated with lower bone mineral density (BMD), larger bone area, and poorer trabecular microarchitecture. In type 1 diabetes, poor glycemic

control, skin AGE accumulation, and microvascular complications, particularly reduced renal function, are associated with deficits in bone microarchitecture as well as lower BMD [14].

Insulin deficiency, poor glycemic control, oxidative stress, and impaired Wnt signaling contribute to compromised skeletal integrity in type 1 diabetes (T1D).
The accumulation of advanced glycation end products (AGEs) and chronic kidney disease exert additional adverse effects on bone metabolism, independently of glycemic control itself. Individuals with long-standing T1D but without vascular complications have a significantly lower risk of osteoporosis and fractures, suggesting a close association between preserved bone health and protection against microvascular complications [15].

The impact of type 2 diabetes on bone homeostasis

T2DM negatively affects trabecular bone mass, while cortical bone mass is increased. The number and function of bone-forming osteoblast is reduced. In addition, vitamin D serum levels are decreased, which alters calcium and phosphate homeostasis. Osteoblasts derive from MSC that favor differentiating into fat-storing adipocytes in T2DM leading to bone marrow adiposity and increased expression of cytokines and chemokines as well as to an elevated amount of free unsaturated fatty acids. This results in increased inflammation leading to accumulation of pro-inflammatory M1 macrophages and reduced switch into anti-inflammatory M2 macrophages. The network of osteocytes is reduced due to an increased apoptosis rate. They increase their expression of sclerostin, an inhibitor of osteoblast function, and RANKL, a promoter of osteoclastogensis. FGF-23, a phosphaturic hormone, is additionally increased. Effects on osteoclasts are controversial in the literature, but T2DM is generally accepted to reduce bone turnover and thus also osteoclast function. The amount of endothelial progenitor cells (EPC) is reduced in T2DM leading to vessel permeability. In addition, T2DM causes microhypoxia in bone niche, which in turn increases inflammation. T2DM patients have an increased risk of falls and fractures due to reduced bone quality indicated by an increased formation of advanced glycation end-products (AGEs) and cortical porosity.

A lower trabecular bone score (TBS) in individuals with T2D further indicates impaired trabecular microarchitecture and may contribute to a more accurate assessment of fracture risk. Therefore, the assessment of bone health in individuals with T2D should include not only BMD but also diabetes duration and glycaemic control, the presence of complications, glucose-lowering therapy, a history of falls and fractures, and, when available, TBS.

Effects of Type 2 Diabetes on Bone Metabolism

The adverse effects of type 2 diabetes on bone metabolism and bone quality include the following:

- Chronic hyperglycemia promotes the formation and accumulation of advanced glycation end products (AGEs) within the bone matrix.
- AGEs reduce osteoprotegerin production and inhibit the Wnt/β-catenin signaling pathway, which is essential for osteoblast differentiation and function.
- They increase the expression of sclerostin and Dickkopf-1 (DKK-1), inhibitors of Wnt/β-catenin signaling, and enhance the activity of degradation-complex components, including glycogen synthase kinase 3β (GSK-3β).
- By forming nonenzymatic cross-links between type I collagen molecules, AGEs impair bone elasticity, strength, and biomechanical stability.
- Hyperglycemia increases oxidative stress and RANKL expression, thereby potentially promoting osteoclastogenesis and bone resorption.
- Osteoblast differentiation and function are simultaneously impaired, resulting in reduced bone formation and disturbed bone remodeling.
- The overall consequence is deterioration of bone microarchitecture and quality, with increased skeletal fragility and fracture risk, even when bone mineral density is normal or increased [16].

WNT/β-catenin signaling and osteoporosis

- WNT proteins (*Wingless-related integration site proteins*) constitute a family of secreted signaling glycoproteins that regulate the proliferation, differentiation, maturation, and survival of osteoblast-lineage cells. The canonical WNT/β-catenin signaling pathway is therefore essential for bone formation and skeletal homeostasis.
- When the WNT/β-catenin pathway is inactive, β-catenin is continuously phosphorylated by the intracellular degradation complex, which includes glycogen synthase kinase 3β (GSK-3β), and subsequently degraded by the proteasome. Consequently, cytoplasmic β-catenin levels remain low.
- When the pathway is activated, WNT ligands bind to Frizzled receptors and LRP5/6 coreceptors, leading to inhibition of the β-catenin degradation complex. β-Catenin is subsequently stabilized and accumulates in the cytoplasm before translocating into the nucleus, where it interacts with TCF/LEF transcription factors and activates the transcription of genes involved in osteoblastogenesis and bone formation.
- Activation of WNT/β-catenin signaling promotes osteoblast differentiation, proliferation, and survival, enhances bone-matrix formation, and increases osteoprotegerin expression, thereby indirectly suppressing osteoclastogenesis.
- Conversely, inhibition of this pathway—particularly by sclerostin and Dickkopf-1 (DKK-1)—reduces osteoblast differentiation and bone formation and may contribute to bone loss and the development of osteoporosis.
- Experimental enhancement of β-catenin signaling increases osteoblast number and bone formation, whereas reduced β-catenin activity produces the opposite effects. However, β-catenin activity must be precisely regulated because its biological effects depend on the cell type, stage of differentiation, and intensity of signaling [17, 18].

The Role of Sclerostin in Bone Formation

- Sclerostin is a glycoprotein produced predominantly by osteocytes and is an important negative regulator of bone formation.
- Sclerostin inhibits the canonical WNT/β-catenin signaling pathway by binding to the low-density lipoprotein receptor-related proteins LRP5 and LRP6, which function as WNT coreceptors on osteoblast-lineage cells. Inhibition of this pathway suppresses osteoblast differentiation and activity, ultimately reducing bone formation.
- Administration of an anti-sclerostin antibody neutralizes the inhibitory effects of sclerostin and reactivates WNT/β-catenin signaling. This stimulates osteoblast activity and increases bone formation.
- Activation of WNT/β-catenin signaling also increases the expression of osteoprotegerin (OPG). By binding to RANKL and preventing its interaction with RANK, OPG inhibits osteoclast differentiation and activation, thereby reducing bone resorption [19].
- Romosozumab, a humanized monoclonal antibody against sclerostin, has a dual effect on bone remodeling: it markedly increases bone formation and, to a lesser extent, decreases bone resorption.
- In postmenopausal women with osteoporosis and a high or very high fracture risk, romosozumab significantly increases bone mineral density and reduces the risk of vertebral and clinical fractures [20].
- In women with osteoporosis and type 2 diabetes, a post hoc analysis of the ARCH trial demonstrated that 12 months of romosozumab followed by alendronate produced greater improvements in lumbar spine areal bone mineral density and tissue thickness–adjusted trabecular bone score than alendronate alone. These findings suggest that romosozumab may improve bone strength in this high-risk population [21, 22].

Scientific clarification: It would be more accurate to avoid stating that fracture-risk reduction with romosozumab has been specifically demonstrated in patients with diabetes. Although fracture reduction has been confirmed in the overall osteoporosis population, studies in patients with type 2 diabetes have primarily demonstrated improvements in bone mineral density and trabecular bone score; diabetes-specific randomized trials with fracture reduction as the primary endpoint are still lacking.

Effects of glucose-lowering therapies on bone health

Glucose-lowering medications may exert neutral, potentially beneficial, or adverse effects on bone metabolism and fracture risk. These skeletal effects should be considered when individualizing treatment, particularly in older adults and in patients with osteoporosis, previous fragility fractures, recurrent hypoglycaemia, or a high risk of falls.

Metformin, dipeptidyl peptidase-4 inhibitors (DPP-4 inhibitors), and glucagon-like peptide-1 receptor agonists (GLP-1 RAs) generally appear to have neutral or

potentially beneficial effects on bone mineral density (BMD) and fracture risk. Incretin-based therapies may influence bone remodelling through direct and indirect mechanisms, including modulation of osteoblast and osteoclast activity. They may also partly counteract the bone loss accompanying weight reduction; however, the skeletal effects of substantial or rapid pharmacologically induced weight loss require further investigation.

Most sodium–glucose cotransporter 2 inhibitors (SGLT2 inhibitors) also appear to have an overall neutral skeletal safety profile. No increased fracture risk was observed with empagliflozin in EMPA-REG OUTCOME or with dapagliflozin in DECLARE–TIMI 58. Although an increased incidence of fractures was initially reported with canagliflozin in the CANVAS Program, this finding was not reproduced in the subsequent CREDENCE trial. Therefore, the early fracture signal associated with canagliflozin has not been consistently demonstrated across clinical trials and should not necessarily be regarded as a class effect of SGLT2 inhibitors.

In contrast, thiazolidinediones exert well-established adverse effects on skeletal health. By promoting adipogenic rather than osteogenic differentiation of mesenchymal stem cells, these agents reduce osteoblast activity and bone formation, decrease BMD, and increase fracture risk, particularly among postmenopausal women. Consequently, thiazolidinediones should generally be avoided or used with considerable caution in individuals at high risk of skeletal fragility.

Sulfonylureas have also been associated with an increased risk of nonvertebral fractures. This relationship may be mediated predominantly by hypoglycaemia-related falls rather than by a direct adverse effect on bone tissue. A similar distinction is important when evaluating insulin therapy. In T2D, insulin use is associated with increased fracture risk, especially at distal skeletal sites; however, this association may reflect longer diabetes duration, greater disease severity, a higher burden of complications, and an increased risk of hypoglycaemia and falls rather than a direct detrimental effect of insulin on bone [23].

In T1D, insulin replacement is essential and may have beneficial skeletal effects because insulin is an anabolic hormone for bone. Adequate insulin treatment and improved glycaemic control have been associated with higher BMD, particularly in individuals without advanced microvascular complications such as retinopathy. Nevertheless, intensive glycaemic treatment should be balanced against the risk of hypoglycaemia, especially in older adults and those susceptible to falls.

The relationship between glycaemic control and fractures may be J-shaped. Chronic hyperglycaemia contributes to impaired bone formation, accumulation of advanced glycation end-products, deterioration of bone material properties, and development of microvascular complications. Conversely, excessively intensive glycaemic control may increase fracture risk through recurrent hypoglycaemia and falls. Glycaemic targets should therefore be individualized according to age, diabetes duration, comorbidities, fracture risk, functional status, and susceptibility to hypoglycaemia.

Although prevention and treatment of vascular complications would theoretically be expected to preserve bone health, direct evidence demonstrating a reduction in fracture incidence remains limited. Selection of glucose-lowering therapy in patients at increased skeletal risk should consequently incorporate not only glycaemic efficacy and cardiorenal benefits but also the medication's effects on body weight, hypoglycaemia, falls, BMD, and fracture risk.

Overall, metformin, DPP-4 inhibitors, GLP-1 receptor agonists, and most SGLT2 inhibitors have predominantly neutral or potentially beneficial skeletal profiles, whereas thiazolidinediones—and, mainly through hypoglycaemia and falls, sulfonylureas and insulin—require particular caution in individuals at increased fracture risk [23].

Bone Health: American Diabetes Association (ADA) 2025 Recommendations

*Assess fracture risk in older adults with diabetes as a part of routine care in diabetes clinical practice, according to risk factors and comorbidities**.** A

***** Monitor bone mineral density using dual-energy X-ray absorptiometry in older adults with diabetes (aged ≥ 65 years) and younger individuals with diabetes and multiple risk factors every 2–3 years A

***** Consider the potential adverse impact on skeletal health when selecting pharmacological options to lower glucose levels in people with diabetes. Avoiding medications with a known association with higher fracture risk (e.g., thiazolidinediones and sulfonylureas) is recommended, particularly for those at elevated risk for fractures. B

***** To reduce the risk of falls and fractures, glycemic management goals should be individualized for people with diabetes at a higher risk of fracture. C Prioritize use of glucose-lowering medications that are associated with low risk for hypoglycemia to avoid falls. B

***** Advise people with diabetes on their intake of calcium (1,000–1,200 mg/day) and vitamin D to ensure it meets the recommended daily allowance for those at risk for fracture, either through their diet or supplemental means. B

***** Antiresorptive medications and osteoanabolic agents should be recommended for older adults with diabetes who are at higher risk of fracture, including those with low bone mineral density with a T-score ≤ -2.0, history of fragility fracture, or elevated Fracture Risk Assessment Tool score (≥ 3% for hip fracture or ≥ 20% for major osteoporotic fracture). B(24)

Bone mineral density testing should be considered an integral component of fracture-risk assessment in individuals with diabetes. The American Diabetes Association recommends BMD assessment in all adults with diabetes aged ≥65 years, as well as in postmenopausal women and men aged ≥ 50 years who have sustained an adult-age fracture or have additional risk factors for skeletal fragility. Diabetes-specific factors warranting earlier assessment include long disease duration, inadequate glycaemic

control, recurrent hypoglycaemia, treatment with medications associated with hypoglycaemia or adverse skeletal effects, microvascular complications, and frequent falls [24].

Table 1. Indications for bone mineral density testing in individuals with diabetes

Population/clinical category	Indications for BMD testing
Older adults with diabetes	All individuals aged ≥65 years
Postmenopausal women and men aged ≥50 years	A history of fracture sustained during adulthood
Postmenopausal women and men aged ≥50 years without a previous fracture	The presence of one or more diabetes-related or general risk factors for skeletal fragility
Diabetes-related risk factors	Frequent hypoglycaemic episodes; diabetes duration >10 years; HbA1c >8%; treatment with insulin, thiazolidinediones, or sulfonylureas; peripheral or autonomic neuropathy; retinopathy; nephropathy; and recurrent falls
Additional risk factor	Current or prolonged glucocorticoid therapy

BMD, bone mineral density; HbA1c, glycated haemoglobin.
Adapted from the American Diabetes Association Standards of Care in Diabetes—2024 [25]

Conclusion

The pathophysiological mechanisms of diabetic osteopathy include chronic hyperglycemia, oxidative stress, impaired Wnt signaling, accumulation of advanced glycation end products (AGEs), and insulin deficiency. Both type of diabetes mellitus are associated with bone fragility, although the underlying mechanisms differ. The pathophysiological mechanisms responsible for bone alterations are less complex in T1DM than in T2DM.In T1DM, the insulin deficiency combined with many other factors lead to a decrease in BMD values and to alterations in bone quality. T1DM is associated with reduced bone mineral density (BMD) and an increased risk of fractures, independently of traditional risk factors. The situation is more complex in T2DM, as BMD is elevated and the bone quality alterations are multifactorial .In individuals with T2DM, despite normal or increased BMD, skeletal integrity may be significantly compromised, highlighting the importance of assessing bone quality rather than bone mass alone. Both T2DM and osteoporosis are affected by aging and changes in lifestyle These two clinical entities quite often coexist and the medications used for each one affects the course of the other .Certain classes of glucose-lowering medications may additionally affect skeletal metabolism, which should be taken into consideration when making therapeutic decisions. Fracture risk assessment and evaluation of bone metabolism should be integrated into the standard care of individuals with diabetes mellitus.Patients with coexisting diabetes mellitus and osteoporosis should be managed in an optimal way according to scientific evidence.

References

[1] International Diabetes Federation. *IDF Diabetes Atlas*. 11th ed. Brussels: International Diabetes Federation; 2025. ISBN: 978-2-930229-96-6.

[2] International Osteoporosis Foundation. *Epidemiology of osteoporosis and fragility fractures*. Available at: https://www.osteoporosis.foundation/facts-statistics/epidemiology-of-osteoporosis-and-fragility-fractures. Accessed September 14, 2026.

[3] Aksentić V, Popović-Pejičić S, Rašeta N, Krčum B. Prevalencija osteoporoze i najčešći faktori rizika kod pacijenata liječenih u Zavodu za fizikalnu medicinu i rehabilitaciju "Dr Miroslav Zotović" u Banjoj Luci. V fizijatriski dani Srbije i Crne Gore, Igalo, 2006; Zbornik radova: 17-24

[4] Ferrari SL, Abrahamsen B, Napoli N, Akesson K, Chandran M, Eastell R, et al.; Bone and Diabetes Working Group of the International Osteoporosis Foundation. Diagnosis and management of bone fragility in diabetes: an emerging challenge. *Osteoporosis International*. 2018;29(12):2585–2596. doi: 10.1007/s00198-018-4650-2.

[5] Popović- Pejičić S. Prevencija i tretman dijabetesa. Prevencija i kontrola osteoporoze. Prevencija i kontrola hiperlipoproteinemije. Prevencija i kontrola gojaznosti. U Vulić D, Babić N. Hronične bolesti-Prevencija i kontrola. Banja Luka, Medicinski fakultet, Univerzitet u Banjoj Luci, 2011; ISBN 978-99938-42-58-3.

[6] Sharma P, Sharma RK, Gaur K. Understanding the impact of diabetes on bone health: A clinical review. *Metabolism Open*. 2024;24:100330. doi: 10.1016/j.metop.2024.100330. PMID: 39606009; PMCID: PMC11600011.

[7] Ali A, Flatt PR, Irwin N. Gut-Derived Peptide Hormone Analogues and Potential Treatment of Bone Disorders in Obesity and Diabetes Mellitus. *Clinical Medicine Insights: Endocrinology and Diabetes*. 2024;17:1–11. doi: 10.1177/11795514241238059.

[8] Popović-Pejičić S, Aksentić V, Rašeta N, Todorović R. Odnos indeksa tjelesne mase i mineralne gustine kosti kod postmenopauzalnih žena.Scripta Medica,Banja Luka , 2007; 38 (2): 59-62.

[9] 9.Rašeta N, Aksentić V, Popović-Pejičić S. Značaj biohemijskih pokazatelja koštanog metabolizma u ranom praćenju efikasnosti alendronata u liječenju postmenopauzalne osteporoze. Acta Rheumatologica Belgradensia 2006; Godište 36 (suppl 1): 125-127.

[10] Miličević S, Bijelić R, Krivokuća V, Bojić M, Popović-Pejičić S, Bojanić N. Correlation of the Body Mass Index and Calcium Nephrolithiasis in Adult Population .Med Arh 2013; 67(6):393-396. doi: 10.5455/medarh.2013.67.423-427

[11] Sheu A, White CP, Center JR. Bone metabolism in diabetes: a clinician's guide to understanding the bone–glucose interplay. Diabetologia. 2024;67(8):1493–1506. doi: 10.1007/s00125-024-06172-x.

[12] Gregory NS, Burghardt AJ, Backlund JYC, Rubin MR, Bebu I, Braffett BH, Kenny DJ, Link TM, Kazakia GJ, Barnie A, Lachin JM, Gubitosi-Klug R, de Boer IH, Schwartz AV; DCCT/EDIC Research Group. Diabetes risk factors and bone microarchitecture as assessed by high-resolution peripheral quantitative computed tomography in adults with long-standing type 1 diabetes. *Diabetes Care*. 2024;47(9):1548–1558. doi: 10.2337/dc23-0839.

[13] Palui R, Pramanik S, Mondal S, Ray S. Critical review of bone health, fracture risk and management of bone fragility in diabetes mellitus. *World Journal of Diabetes*. 2021;12(6):706–729. doi: 10.4239/wjd.v12.i6.706.

[14] Picke AK, Campbell G, Napoli N, Hofbauer LC, Rauner M. Update on the impact of type 2 diabetes mellitus on bone metabolism and material properties. *Endocrine Connections*. 2019;8(3):R55–R70. doi: 10.1530/EC-18-0456.

[15] Sharma P, Sharma RK, Gaur K. Understanding the impact of diabetes on bone health: A clinical review. Metabol Open. 2024;24:100330.
[16] Hu L, Chen W, Qian A, Li YP. Wnt/β-catenin signaling components and mechanisms in bone formation, homeostasis, and disease. *Bone Research.* 2024;12:39. doi: 10.1038/s41413-024-00342-8.
[17] Canalis E. Wnt signalling in osteoporosis: mechanisms and novel therapeutic approaches. *Nature Reviews Endocrinology.* 2013;9(10):575–583. doi: 10.1038/nrendo.2013.154.
[18] Hu L, Chen W, Qian A, Li YP. Wnt/β-catenin signaling components and mechanisms in bone formation, homeostasis, and disease. *Bone Research.* 2024;12:39. doi: 10.1038/s41413-024-00342-8.
[19] Cosman F, Crittenden DB, Adachi JD, et al. Romosozumab treatment in postmenopausal women with osteoporosis. *New England Journal of Medicine.* 2016;375(16):1532–1543. doi: 10.1056/NEJMoa1607948.
[20] Saag KG, Petersen J, Brandi ML, et al. Romosozumab or alendronate for fracture prevention in women with osteoporosis. *New England Journal of Medicine.* 2017;377(15):1417–1427. doi: 10.1056/NEJMoa1708322.
[21] Ferrari S, Betah D, Feldman RG, Langdahl BL, Oates M, Timoshanko J, Wang Z, Dhaliwal R. Romosozumab improves tissue thickness–adjusted trabecular bone score in women with osteoporosis and diabetes. *Journal of Clinical Endocrinology & Metabolism.* 2025;110(10):2861–2868. doi: 10.1210/clinem/dgae862.
[22] Zawada A, Ratajczak AE, Rychter AM, Szymczak-Tomczak A, Dobrowolska A, Krela-Kaźmierczak I. Treatment of Diabetes and Osteoporosis—A Reciprocal Risk? *Biomedicines.* 2022;10(9):2191. doi: 10.3390/biomedicines10092191.
[23] Sheu A, White CP, Center JR. Bone metabolism in diabetes: a clinician's guide to understanding the bone–glucose interplay. Diabetologia. 2024;67(8):1493–1506. doi: 10.1007/s00125-024-06172-x.
[24] Comprehensive Medical Evaluation and Assessment of Comorbidities: *Standards of Care in Diabetes - 2025*. *Diabetes Care* 2025;48(Suppl. 1):S59-S85
[25] American Diabetes Association Professional Practice Committee. 4. Comprehensive medical evaluation and assessment of comorbidities: Standards of Care in Diabetes—2024. Diabetes Care. 2024;47(Suppl 1):S52–S76. doi: 10.2337/dc24-S004

DIJABETES MELITUS I ZDRAVLJE KOSTI: SAVREMENI KONCEPT POVEZANOSTI SA OSTEOPOROZOM

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Sažetak. *Dijabetes melitus (DM) i osteoporoza su hronične bolesti sa rastućom prevalencijom. U svijetu 589 miliona odraslih osoba živi sa DM, dok osteoporoza pogađa približno 500 miliona ljudi, uključujući 21,2% žena i 6,3% muškaraca starijih od 50 godina. Ova oboljenja često koegzistiraju, zbog čega se koristi pojam dijabetesna osteopatija (DO), koji obuhvata strukturne i funkcionalne poremećaje kosti nastale usljed hronične hiperglikemije i drugih metaboličkih poremećaja povezanih sa dijabetesom.Patofiziologija DO uključuje hroničnu hiperglikemiju, oksidativni stres, poremećaj Wnt signalnog puta, nakupljanje krajnjih produkata uznapredovale glikacije (AGEs) te deficit ili rezistenciju na insulin. Dijabetes melitus tipa 1 (T1DM) i tipa 2 (T2DM) imaju različite profile skeletnog rizika. T1DM je povezan sa smanjenom mineralnom gustinom kosti (BMD) i povećanim rizikom od fraktura. Kod T2DM, skeletni integritet može biti značajno narušen uprkos normalnoj ili povećanoj BMD, što pokazuje da je kvalitet kosti, a ne samo koštana masa, klinički važan. Rizik od frakture kuka povećan je približno 1,3–1,7 puta, što ukazuje da BMD potcjenjuje skeletnu fragilnost u T2DM.T2DM se najčešće karakteriše sniženim koštanim prometom, poremećenom formacijom kosti, izmijenjenom mikroarhitekturom i lošijim materijalnim osobinama kosti, čemu doprinose hormonski poremećaji, inflamacija, vaskularne komplikacije i poremećeni ćelijski signalni putevi. Frakture su povezane sa sporijim oporavkom, većom učestalošću komplikacija i povećanom smrtnošću.Antihiperglikemijska terapija takođe može uticati na skeletno zdravlje. Metformin, inhibitori dipeptidil-peptidaze 4 i agonisti receptora glukagonu sličnog peptida 1 uglavnom imaju neutralne ili potencijalno povoljne skeletne efekte. Tiazolidindioni povećavaju rizik od fraktura, dok preparati sulfonilureje i insulin mogu povećati taj rizik djelimično posredstvom hipoglikemijom izazvanih padova. Signal povećanog rizika od fraktura zabilježen uz kanagliflozin u studiji CANVAS nije potvrđen u studiji CREDENCE niti u objedinjenim analizama. Stoga procjena rizika od fraktura i evaluacija zdravlja kosti treba da budu integrisani dio standardne njege osoba sa dijabetesom.*

Ključne riječi: *Dijabetes melitus , osteoporoza, BMD (koštana mineralna gustina), frakture ,antihiperglikemijski lijekovi*