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REVIEW ARTICLE

Managing Bone Fragility in Older Adults with Diabetes: Pathophysiology, Assessment, and Therapeutic Considerations

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Abstract

Older adults with diabetes mellitus, encompassing both type 1 diabetes (T1D) and type 2 diabetes (T2D), face a substantially elevated risk of fragility fractures, contributing significantly to morbidity and mortality in this vulnerable population. The underlying pathophysiology differs between the two types: T1D is typically characterized by reduced bone mineral density (BMD) stemming from insulinopenia, whereas T2D often presents with normal or even high BMD but compromised bone quality due to factors, including altered microarchitecture, accumulation of advanced glycation end products (AGEs), and low bone turnover. These distinct mechanisms create challenges for accurate fracture risk assessment, as standard tools such as dual-energy X-ray absorptiometry (DXA)-measured BMD and the Fracture Risk Assessment Tool (FRAX) often underestimate the true risk, particularly in T2D. Effective management necessitates a comprehensive, individualized approach. This includes optimizing glycemic control while minimizing hypoglycemia, implementing lifestyle modifications such as adequate nutrition (calcium, vitamin D, protein) and appropriate exercise, and crucially, proactive fall prevention strategies. Careful consideration must be given to the selection of antidiabetic medications, avoiding agents known to harm bone (e.g., thiazolidinediones) and preferring those with neutral or potentially beneficial skeletal effects (e.g., metformin, dipeptidyl peptidase-4 inhibitors [DPP-4i], glucagon-like peptide-1 receptor agonists [GLP-1 RAs]). Osteoporosis pharmacotherapies, including antiresorptive (bisphosphonates, denosumab) and anabolic agents (teriparatide, abaloparatide, romosozumab), appear effective in patients with diabetes largely on the basis of post hoc analyses and observational data, although evidence specific to this population remains limited. Integrating geriatric principles, such as assessing frailty and polypharmacy, is essential for optimizing care and improving outcomes for older adults with diabetes and bone fragility.

1 Introduction

The confluence of aging populations and the escalating prevalence of diabetes mellitus presents a significant global public health challenge. Type 2 diabetes (T2D), in particular, affects a substantial proportion of older adults, with estimates suggesting that around 20% of individuals over 60 years worldwide have the condition [1]. With advancing age, the prevalence of diabetes increases markedly. In 2024, it was reported as 1.9% among adults aged 20–24 years and is projected to rise to 2.2% by 2050, whereas it peaked at 24.8% among those aged 75–79 years in 2024 and is expected to reach 25.4% by 2050 [2]. In older adults, another very significant concern is fragility fractures. Fragility fractures are defined as fractures resulting from low-energy trauma equivalent to a fall from standing height or less, and they represent a major source of morbidity, mortality, and healthcare expenditure in older adults [3]. Globally, millions experience such fractures annually, leading to pain, disability, loss of independence, and increased mortality risk [3].

It is now unequivocally established that both type 1 diabetes (T1D) and T2D are independent risk factors for fragility fractures [4]. While the relative risk increase is generally higher in T1D compared with T2D [5], the sheer prevalence of T2D makes it a major contributor to the overall fracture burden in older populations. Furthermore, patients with diabetes often experience worse post-fracture outcomes, including higher rates of complications such as infection, delayed healing, functional decline, and increased mortality [5, 6].

Managing bone health in older adults with diabetes is complicated by several factors. A key challenge arises from the distinct pathophysiology affecting bone in T1D versus T2D. While T1D is often associated with lower bone mineral

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Key Points

Older adults with both type 1 and type 2 diabetes have a significantly higher risk of bone fractures compared with nondiabetic individuals, driven by distinct underlying impairments in bone quantity (T1D) and quality (T2D).

Standard fracture risk assessment tools, including bone density scans (DXA) and FRAX, often underestimate fracture risk in diabetes; comprehensive evaluation incorporating fall risk, diabetes-specific factors, and potential assessment adjustments is necessary.

Management requires a personalized strategy focusing on safe glycemic control, selecting bone-friendly antidiabetic medications, promoting adequate nutrition and exercise, preventing falls, and utilizing osteoporosis treatments when indicated on the basis of individualized risk.

density (BMD), emerging evidence suggests that alterations in bone quality may also contribute to fracture risk, albeit to a lesser extent than in T2D [7]. In contrast, T2D frequently presents a paradox: Patients exhibit normal or even elevated BMD measured by standard dual-energy X-ray absorptiometry (DXA), yet still suffer from increased fracture rates [4]. This suggests that factors beyond bone mass, collectively termed "bone quality"—encompassing microarchitecture, material properties, and bone turnover—are significantly impaired in T2D [8]. Consequently, standard risk assessment tools such as DXA and the Fracture Risk Assessment Tool (FRAX) often underestimate the true fracture risk in individuals with diabetes, particularly T2D [9].

This review aims to provide a comprehensive overview of the current understanding of bone fragility in older adults with T1D and T2D. It will delve into the distinct and shared pathophysiological mechanisms, discuss the challenges in risk assessment, and summarize evidence-based management strategies. A particular focus will be placed on pharmacological considerations, including the skeletal effects of various antidiabetic medications and the efficacy and safety of osteoporosis therapies within this specific patient population. Emerging concepts and future research directions will also be explored.

Literature search and study selection: This invited narrative review is based on a comprehensive, nonsystematic literature search conducted in PubMed and Web of Science. Relevant articles published in English were identified using combinations of keywords, including diabetes, bone health, bone quality, osteoporosis, and fracture risk. Priority was given to recent review articles, clinical studies, and landmark papers that addressed pathophysiological mechanisms, fracture risk assessment, and clinical management of bone health in older adults with diabetes. Articles were selected on the basis of their relevance, scientific quality, and clinical significance

2 Pathophysiology of Increased Bone Fragility in Older Adults with Diabetes

The increased propensity for fractures in individuals with diabetes stems from complex alterations in bone metabolism, structure, and material properties. While hyperglycemia and its consequences, such as the formation of advanced glycation end products (AGEs), represent common detrimental factors in both T1D and T2D, the predominant mechanisms driving bone fragility differ significantly between the two conditions [4]. T1D primarily impacts bone quantity, leading to lower BMD, whereas T2D predominantly affects bone quality, resulting in compromised microarchitecture and material strength despite often normal or even elevated BMD [4].

2.1 Mechanisms Specific to Type 1 Diabetes

The cornerstone of bone pathology in T1D is the autoimmune destruction of pancreatic β cells, leading to absolute insulin deficiency [10]. Insulin is a potent anabolic hormone for the skeleton, stimulating osteoblast proliferation and differentiation, promoting collagen synthesis, and inhibiting osteoblast apoptosis [11]. The absence of this crucial anabolic signal in T1D directly impairs bone formation and contributes to a state of reduced bone mass [4].

Consequently, T1D is classically associated with reduced BMD compared with age-matched controls, an effect particularly noted in cortical bone [4]. Studies have reported lower BMD predominantly at the femur, with potentially less impact on vertebral BMD [8]. Alterations in bone geometry, such as reduced cortical thickness alongside increased cross-sectional area, have also been described, suggesting adaptive changes alongside deficits [12]. However, the observed reduction in BMD, while significant, often does not fully account for the magnitude of the increased fracture risk seen in T1D, pointing toward additional impairments in bone quality [4]. As such, in the standard FRAX model, type 1 diabetes is considered under secondary osteoporosis and can therefore be selected as a fracture risk-increasing factor in the risk assessment [13].

Other hormonal factors contribute to bone fragility in T1D. Insulin deficiency leads to reduced levels and/or action of insulin-like growth factor 1 (IGF-1), another critical regulator of osteoblast function and bone formation [14]. Furthermore, amylin, a hormone co-secreted with insulin by β cells that normally inhibits osteoclasts and stimulates

osteoblasts, is also deficient in T1D, potentially exacerbating the imbalance in bone remodeling [4].

A critical aspect influencing lifelong skeletal health in T1D is the typical age of onset. As T1D often manifests during childhood or adolescence, it coincides with the crucial period of peak bone mass accrual [15]. The lack of adequate anabolic signaling during these formative years likely results in the attainment of a lower peak bone mass. This establishes a weaker skeletal foundation, making individuals with T1D inherently more susceptible to age-related bone loss and subsequent fractures later in life, irrespective of subsequent glycemic control or the development of complications. This early impact on skeletal development represents a fundamental difference compared with T2D, which usually develops after peak bone mass has been achieved.

2.2 Mechanisms Specific to Type 2 Diabetes: The Bone Quality Paradox

T2D presents a more complex picture regarding bone health, often termed the "diabetic bone paradox" [4]. Unlike T1D, patients with T2D frequently exhibit normal or even increased BMD, particularly at the hip and spine [1]. This is often attributed to factors associated with T2D, such as higher body weight leading to increased mechanical loading, and the effects of hyperinsulinemia, particularly in the earlier stages of the disease [8].

Despite preserved or elevated BMD, individuals with T2D consistently demonstrate an increased risk of fragility fractures [4]. This discrepancy underscores that BMD, as measured by DXA, is an inadequate measure of bone strength in T2D. The increased fracture susceptibility is instead driven by impairments in "bone quality," a term encompassing microarchitecture, material properties, and bone turnover dynamics [4]. This constellation of findings is sometimes referred to as "diabetic osteopathy" [8]. As such, some authors suggest signifying T2D equivalent to the risk with rheumatoid arthritis in classical FRAX models [16]. The newer FRAXplus also integrated T2D as a risk factor for fracture estimation [17].

Evidence for microarchitectural deterioration comes from various imaging modalities. Trabecular bone score (TBS), a texture parameter derived from lumbar spine DXA images that reflects trabecular microarchitecture, is consistently found to be lower in individuals with T2D compared with controls, even in those with prediabetes [18]. High-resolution peripheral quantitative computed tomography (HR-pQCT) studies have provided more direct evidence, revealing increased cortical porosity, particularly at the radius and tibia, in older individuals and postmenopausal women with T2D, especially those with fragility fractures [4]. This increased porosity weakens the cortical shell and reduces overall bone strength [14]. Notably, poorer cortical bone quality has been linked to the presence of microvascular disease [5].

Beyond architecture, the intrinsic material properties of the bone tissue itself are compromised in T2D. In vivo bone microindentation studies have demonstrated a reduced Bone Material Strength index (BMSi) in patients with T2D compared with controls, suggesting increased brittleness [14]. This impairment in material strength is thought to be significantly influenced by the accumulation of AGEs within the bone matrix [14].

Furthermore, T2D is generally characterized as a state of low bone turnover [8]. Meta-analyses and histomorphometry studies consistently show reduced levels of both bone formation and resorption markers, as well as a decreased bone formation rate and increased mineralization lag time [8]. Elevated levels of sclerostin, an inhibitor of the Wnt signaling pathway crucial for bone formation, have been observed in T2D and may contribute to this low turnover state [8]. Reduced turnover can impair the repair of microdamage accumulation, further contributing to bone fragility [12].

The existence of the "diabetic paradox" carries significant clinical implications. It clearly demonstrates that relying solely on BMD measurements is insufficient and potentially misleading for assessing fracture risk in patients with T2D. Clinical attention must shift toward understanding and, where possible, assessing the factors that influence bone *quality*—including microarchitecture, material properties, and turnover rates—as these appear to be the primary determinants of skeletal fragility in this patient population.

2.3 Shared Mechanisms and Contributing Factors

While T1D and T2D have distinct primary drivers of bone fragility, several underlying mechanisms contribute to impaired bone health in both types, largely stemming from the consequences of chronic hyperglycemia and associated metabolic disturbances.

Hyperglycemia itself exerts direct detrimental effects on bone cells. High glucose levels can inhibit the function of osteoblasts and osteocytes, impairing their ability to synthesize bone matrix components and orchestrate mineralization [4]. Furthermore, hyperglycemia can promote osteoblast apoptosis (programmed cell death) and senescence (cellular aging), further reducing bone formation capacity [10, 16, 19]. In this context, recent experimental data indicate that osteocyte senescence represents a distinct and particularly important mechanism contributing to skeletal fragility in diabetes, especially in T2D. Osteocytes in diabetic conditions have been shown to develop a senescence-associated secretory phenotype characterized by a proinflammatory profile, reflecting accelerated cellular ageing and potentially impairing their ability to regulate bone remodelling. On the basis of these observations, diabetes—especially T2D—has

been proposed as a model of accelerated skeletal ageing, in which increased osteocyte senescence may constitute a key mechanism underlying low bone turnover and deterioration of bone quality, a process that is likely to be particularly relevant in older adults with long-standing disease [9].

A major consequence of chronic hyperglycemia is the nonenzymatic glycation of proteins and lipids, leading to the formation and accumulation of advanced glycation end products (AGEs) [4]. Bone collagen, the primary structural protein of the organic matrix, is particularly susceptible to glycation. The accumulation of AGEs forms abnormal cross-links within and between collagen molecules, leading to increased matrix stiffness, reduced elasticity and toughness, and ultimately, increased bone brittleness and fragility [4]. Beyond these direct structural effects, AGEs also impair cellular function. They can inhibit osteoblast differentiation and mineralization processes [4]. Moreover, AGEs interact with their receptor (RAGE) on bone cells, triggering intracellular signaling pathways (such as NF-κB) that promote inflammation and oxidative stress, leading to increased osteoclast formation and activity, thus enhancing bone resorption [4]. Higher AGE levels have been correlated with lower TBS and BMSi values, linking them directly to impaired microarchitecture and material strength [14]. The central role of AGEs in directly translating hyperglycemia into poor bone quality makes them a critical factor in diabetic bone disease and a potential focus for future therapeutic interventions.

Diabetes is also recognized as a state of chronic, low-grade inflammation and increased oxidative stress [4]. Elevated levels of proinflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), are commonly found in patients with diabetes, particularly those with obesity [20]. These cytokines disrupt the delicate balance of bone remodeling by stimulating osteoclastogenesis (bone resorption) and inhibiting osteoblast differentiation (bone formation) [4]. Increased production of reactive oxygen species (ROS) further contributes to cellular damage and dysfunction within the bone microenvironment [4].

Alterations in adipose tissue metabolism and signaling also play a role, particularly in T2D. Dysregulation of adipokines, hormones secreted by adipose tissue, may contribute to bone fragility. For instance, levels of adiponectin, which may have anabolic effects on osteoblasts and inhibitory effects on osteoclasts, are often low in T2D [20]. Leptin levels may also be altered, potentially affecting bone resorption and density differentially in cortical versus trabecular bone [20]. Furthermore, there is evidence of increased bone marrow adiposity in diabetes, potentially occurring at the expense of osteoblastogenesis, as both cell types arise from common mesenchymal progenitors [21]. Reduced brown adipose tissue activity, which normally secretes bone-anabolic factors, has also been noted in T2D and obesity [20].

2.4 Impact of Diabetic Complications on Bone Health

The systemic nature of diabetes means that its complications affecting other organ systems can further exacerbate bone fragility and increase fracture risk.

Microvascular complications, including retinopathy, nephropathy, and neuropathy, are consistently linked to poorer skeletal outcomes in both T1D and T2D [22]. Patients with these complications tend to have lower BMD (especially in T1D) [12], increased cortical porosity, detrimental alterations in microarchitecture, and a significantly higher risk of fractures compared with patients with diabetes without complications. In later life, long-standing T1D and the accumulation of diabetes-related complications, particularly microvascular disease and neuropathy, further contribute to impaired bone quality and increased fracture risk. The mechanisms linking microvascular disease to bone fragility likely involve impaired blood supply to the bone (cortical microangiopathy), hindering nutrient delivery and waste removal essential for bone health [12]. Additionally, shared pathogenic factors such as the accumulation of AGEs and chronic inflammation likely contribute to damage in both the microvasculature and the skeleton [23]. The presence of microvascular complications should therefore be considered a significant clinical indicator of heightened underlying bone quality deficits and substantially increased fracture risk, warranting more aggressive screening and preventative measures for bone health.

Recent evidence further supports the concept that skeletal fragility should be considered an additional chronic complication of diabetes, closely linked to the microvascular disease spectrum. In a recent clinical review, Sharma et al. proposed that diabetic bone disease represents a distinct microvascular-related complication, integrating microangiopathy, AGE accumulation, chronic inflammation, and increased fall risk as converging mechanisms leading to fractures [10]. In addition to microvascular disease, clinical evidence also suggests an association between macrovascular complications and skeletal fragility in diabetes. In large population-based cohorts of patients with T2D, a history of atherosclerotic cardiovascular disease—such as ischemic heart disease and stroke—has been identified as an independent predictor of hip and major osteoporotic fractures. These findings indicate that macrovascular disease may act as a clinical marker of increased fracture risk in diabetes, potentially reflecting shared alterations in vascular health and bone remodeling [24].

Diabetic neuropathy has multifaceted effects. Peripheral sensory neuropathy diminishes protective sensation and impairs balance, while autonomic neuropathy can cause orthostatic hypotension; both significantly increase the risk of falls [25]. Motor neuropathy can contribute to muscle

weakness and sarcopenia, further impairing mobility and stability [26].

Diabetic nephropathy, leading to chronic kidney disease (CKD), introduces additional complexities through disturbances in mineral metabolism. Impaired kidney function affects calcium and phosphate homeostasis, vitamin D activation (reduced synthesis of active 1,25-dihydroxyvitamin D), and can lead to secondary hyperparathyroidism, collectively contributing to CKD–mineral and bone disorder (CKD–MBD) [27].

Visual impairment resulting from diabetic retinopathy also significantly increases the risk of falls and subsequent fractures [22]. Cataract, which increases morbidity in DM, also further increases fall risk, contributing to increased fracture risk.

Recent evidence supports these mechanisms; for example, in older adults with T1D, early disease onset and the presence of nephropathy or neuropathy were associated with unfavorable femoral neck bone outcomes, contributing to elevated hip fracture risk [28].

3 Assessing Fracture Risk in the Older Patient with Diabetes

Accurately assessing fracture risk in older adults with diabetes is crucial for implementing timely preventive strategies, yet it presents unique challenges. Standard assessment tools developed for the general population often prove insufficient owing to the complex interplay of factors affecting bone strength and fall propensity in diabetes [9]. Both impaired bone quality, which is not captured by conventional BMD measurements, and a heightened risk of falls contribute significantly to the elevated fracture rates observed in this population [22].

In this regard, FRAX plus has room to improve fracture risk assessment when compared with the original FRAX as it incorporates DM, falls, and other measures to assess bone microarchitecture [17]. However, cost emerges as a limiting issue in its use.

3.1 Fracture Epidemiology in Older Adults with Diabetes

Epidemiological studies consistently demonstrate a significantly increased incidence of fragility fractures in older adults with both T1D and T2D, compared with their nondiabetic counterparts [29]. The elevation in risk is not only particularly pronounced for hip fractures [1] but also affects vertebral and certain nonvertebral sites such as the foot [1]. Data for wrist and proximal humerus fractures are less consistent [30]. T1D generally confers a higher relative risk, and fractures tend to occur at an earlier age compared with T2D or individuals without diabetes [5].

Across all age groups, individuals with T1D have greater fracture risk than their nondiabetic peers; for instance, women aged 40–49 years have an 82% higher risk of any fracture, whereas men aged 60–69 years show a twofold increased risk of overall fractures and more than a fourfold increased risk of hip fractures after adjustment for confounders [31]. These observations are reinforced by meta-analyses demonstrating that hip fracture risk is substantially higher in T1D than in T2D, with nonoverlapping confidence intervals, suggesting a greater magnitude of risk in T1D [32, 33]. Collectively, these findings imply that distinct mechanisms may underlie skeletal fragility in T1D and T2D.

Several factors modulate fracture risk within the diabetic population. Increasing age is a universal risk factor, but its interaction with diabetes can be complex, with some studies suggesting that the relative risk conferred by diabetes may be higher in younger individuals compared with the oldest old, where background risk is already high [5]. Longer duration of diabetes, often cited as greater than 5 or 10 years, is associated with increased risk [5]. Poor glycemic control, typically defined as HbA1c levels above 7% or 8%, is also linked to higher fracture rates, likely reflecting the cumulative burden of hyperglycemia and associated complications [5]. The presence of microvascular and neuropathic complications significantly elevates risk [22]. Insulin use is frequently identified as a risk factor, although this is likely confounded by disease severity, longer duration, and increased risk of hypoglycemia [1]. Some evidence suggests a biphasic pattern in T2D, with risk potentially lower in the initial years after diagnosis before increasing significantly over time [5].

3.2 Challenges with Standard Risk Assessment (BMD, FRAX)

The assessment of fracture risk in older patients with diabetes is hampered by the limitations of standard diagnostic tools when applied to this population. DXA-measured BMD, the cornerstone of osteoporosis diagnosis, is particularly problematic in T2D. As discussed previously (Sect. 2.2), BMD values in T2D are often normal or even elevated, failing to reflect the underlying skeletal fragility [1]. This is because DXA primarily measures bone mass (quantity) and cannot adequately capture the deficits in bone quality—microarchitecture and material properties—that are central to diabetic bone disease [8].

The FRAX tool, which calculates the 10-year probability of major osteoporotic and hip fractures by integrating clinical risk factors with or without femoral neck BMD, also performs suboptimal in diabetes. While T1D is listed as a cause of secondary osteoporosis within the tool [13], T2D is not explicitly included as an input variable. Numerous studies

have demonstrated that FRAX systematically underestimates fracture risk in individuals with diabetes, particularly T2D [34]. Validation studies comparing FRAX predictions to observed fracture incidence in diabetic cohorts consistently show that actual fracture rates are higher than those predicted by the algorithm [35]. This underestimation can be substantial, ranging from 20 to 80% in certain subgroups, such as Hispanic women, Black men, those with long-standing diabetes (> 20 years), and the very old (> 80 years) [35]. The failure of these standard tools to accurately capture risk in patients with diabetes means that clinicians relying solely upon them may fail to identify high-risk individuals who could benefit from preventive interventions. This necessitates a shift in clinical practice toward approaches that specifically account for the impact of diabetes.

3.3 Optimizing Risk Stratification in Diabetes

Given the limitations of standard BMD and FRAX assessments, several strategies have been proposed and investigated to improve fracture risk stratification in patients with diabetes, particularly T2D.

One approach involves adjusting the inputs or outputs of the FRAX calculation. Several methods have been studied (Table 1):

- Rheumatoid arthritis input: Using the "Yes" input for rheumatoid arthritis in the FRAX tool as a surrogate for the presence of T2D. This simple adjustment has been shown to partially attenuate the underestimation of risk, although residual underestimation, particularly for hip fractures, may persist [5].
- Trabecular bone score (TBS) adjustment: Incorporating TBS, an index of lumbar spine microarchitecture derived from DXA, into the FRAX calculation (TBS-adjusted FRAX). Since T2D is associated with lower TBS [18], and low TBS predicts fractures independently of BMD and FRAX, this adjustment can improve risk prediction [17].
- BMD T-score adjustment: Empirically reducing the femoral neck T-score input into FRAX by a fixed amount, typically 0.5 standard deviations [36].
- Age adjustment: Empirically increasing the age input into FRAX by 10 years [37].
- Duration adjustment: The FRAXplus platform allows for adjustments on the basis of the duration of T2D, recognizing its influence on risk [17]. Beyond simple input adjustments, the FRAX Plus tool represents a more diabetes-specific extension of fracture risk assessment. By incorporating diabetes as an explicit risk modifier and accounting for disease duration, FRAX Plus better captures the cumulative skeletal burden of long-standing T2D, thereby reducing the underestimation of fracture risk observed with standard FRAX, particularly for hip fractures.

Comparative studies suggest that each of these adjustments improves FRAX performance compared with the unadjusted score, although no single method appears optimal in all circumstances, and some degree of underestimation may remain, particularly for hip fracture risk [17].

Beyond FRAX adjustments, incorporating diabetes-specific clinical factors into the overall risk assessment is essential. This includes considering the duration of diabetes, level of glycemic control (HbA1c), history of insulin use, and the presence and severity of diabetic complications (neuropathy, nephropathy, retinopathy) [5].

Emerging technologies hold promise for better characterizing bone quality noninvasively. Techniques such as HR-pQCT provide detailed microarchitectural information but are largely confined to research settings [8]. Quantitative ultrasound (QUS) is being explored, with

Table 1 Summary of proposed FRAX adjustments for patients with type 2 diabetes

Adjustment method	Brief description	Supporting evidence snippet IDs	Notes/limitations
Rheumatoid arthritis input	Select "Yes" for RA clinical risk factor as a surrogate for T2D	[5]	Simple; partially corrects risk; may still underestimate hip fracture risk
TBS adjustment	Incorporate trabecular bone score (TBS) value into FRAX calculation (if available)	[16]	Reflects microarchitecture; improves prediction; requires TBS software/availability
T-score reduction	Reduce femoral neck T-score input by 0.5 SD	[35]	Empirical adjustment; improves prediction
Age increase	Increase age input by 10 years	[35]	Empirical adjustment; improves prediction
Duration adjustment (FRAXplus)	Use FRAXplus tool to adjust on the basis of duration of T2D	[16]	Accounts for duration effect; requires access to FRAXplus platform

FRAX fracture risk assessment tool, *RA* rheumatoid arthritis, *SD* standard deviation, *T2D* type 2 diabetes

some recent studies suggesting potential advantages over DXA in discriminating fracture risk in patients with diabetes [38]. Various biomarkers reflecting bone turnover (e.g., P1NP, CTX), AGE accumulation (e.g., pentosidine), inflammation, or novel regulators (e.g., sclerostin, microRNAs [miRNAs]) are under investigation but currently lack sufficient validation for routine clinical use in diabetes-specific risk assessment [9].

3.4 The Critical Role of Falls Assessment

Fractures typically occur as a result of a fall, and older adults with diabetes are particularly vulnerable to falling [22]. Their risk of falling is significantly higher than that of their nondiabetic peers owing to a multitude of contributing factors inherent to the disease and its management [39].

Hypoglycemia, particularly when induced by insulin or sulfonylureas, is a major precipitant of falls owing to its potential to cause confusion, dizziness, and loss of consciousness [22]. Diabetic neuropathy contributes significantly through sensory loss in the feet, impaired proprioception and balance, and muscle weakness. Autonomic neuropathy can lead to orthostatic hypotension, increasing the risk of syncope or near-syncope upon standing [25]. Visual impairment from diabetic retinopathy reduces environmental awareness [40]. Furthermore, older adults with diabetes often have multiple comorbidities, leading to polypharmacy, which itself is a risk factor for falls [40]. Sarcopenia (age-related loss of muscle mass and strength) is accelerated in diabetes, further compromising mobility and stability [40]. Cognitive impairment and frailty, both more prevalent in older adults with diabetes, also increase fall susceptibility [40].

Given this heightened fall risk profile, a comprehensive fall risk assessment should be considered an indispensable component of fracture prevention in older diabetic adults [40, 41]. Identifying and addressing modifiable risk factors through medication review (deprescribing, avoiding high-risk drugs), optimizing vision and blood pressure control, managing neuropathy, implementing home safety modifications, and prescribing appropriate exercise and balance training programs are crucial interventions [40]. The FRAXplus tool incorporates falls history as an adjustment factor, acknowledging its importance [17]. Because falls are such a potent trigger for fractures, particularly hip fractures, effectively managing fall risk may provide one of the most impactful strategies for reducing fracture incidence in this vulnerable population, complementing efforts aimed at improving bone density and quality. Assessment of falls can be performed by World Falls Guideline, which is a comprehensive consensus produced by a multidisciplinary committee [42]. In routine clinical practice, fall risk can be efficiently assessed using simple, validated bedside tests that require minimal time and equipment. The Timed Up and Go (TUG) test, one of the most widely used tools, involves standing up from a chair, walking 3 m, turning, returning, and sitting down; a completion time > 12 s is generally associated with increased fall risk and impaired mobility. The Five Times Sit-to-Stand test provides complementary information on lower-extremity strength and balance, with prolonged completion times indicating higher fall and fracture risk. Additional measures such as usual gait speed ($\leq$ 0.8 m/s), single-leg stance, and tandem stance further assess balance and postural stability [43]. These tests should be interpreted alongside evaluation of orthostatic hypotension, peripheral neuropathy, visual impairment, and medication review to guide targeted fall-prevention strategies in older adults with diabetes. Beyond fall risk, frailty assessment is essential in older adults with diabetes, as frailty affects fracture risk, treatment tolerance, and functional outcomes. In routine clinical practice, simple and rapid validated tools such as the Clinical Frailty Scale [44], Fried Frailty Scale [45], or the Simpler Modified Fried Frailty Scale [46–49] can be applied within a few minutes to identify vulnerable patients. In individuals with moderate-to-severe frailty, antidiabetic treatment should be carefully individualized, and referral for comprehensive geriatric assessment should be considered to prevent further functional decline and loss of autonomy.

4 Current Management Approaches

Managing bone fragility in older adults with diabetes requires a multifaceted strategy that extends beyond glycemic control alone. It encompasses targeted screening, lifestyle modifications focusing on nutrition and exercise, proactive fall prevention, careful selection of antidiabetic therapies considering their skeletal effects, and appropriate use of osteoporosis medications when indicated [5]. Given the heterogeneity of older adults in terms of health status, functional ability, comorbidities, and frailty, an individualized, patient-centered approach is paramount [50].

4.1 Screening and Diagnosis

Identifying individuals at high risk is the first step in prevention. Current guidelines offer recommendations for screening, although their specific applicability to the diabetic population warrants consideration. The American Diabetes Association (ADA) 2024 Standards of Care recommend BMD testing using DXA for all adults aged 65 years and older, aligning with general population guidelines, and also for younger adults with multiple risk factors for fracture [51]. The International Society for Clinical Densitometry (ISCD) provides broader indications for BMD testing based on age (women $\geq$ 65 years, men $\geq$ 70 years) or the presence

of clinical risk factors such as low body weight, prior fracture, or use of high-risk medications (e.g., glucocorticoids) in younger postmenopausal women and men aged 50–69 years [52].

Notably, the ISCD also lists long-term (> 10 years) or poorly controlled diabetes as a condition conferring greater risk for impaired bone health in patients undergoing elective orthopedic surgery, suggesting consideration for DXA testing in that specific context [52].

Reflecting the concern that standard guidelines might not be sufficiently sensitive for the diabetic population, the Bone and Diabetes Working Group of the International Osteoporosis Foundation (IOF) has proposed considering BMD screening for any patient with diabetes-specific risk factors, such as disease duration exceeding 5 years or an HbA1c level above 7.0% [5]. This proactive approach acknowledges the earlier onset and often underestimated nature of fracture risk in diabetes. Despite these recommendations, screening rates remain low, with estimates suggesting only about a third of patients with diabetes undergo bone health evaluations [19].

Once DXA is performed, the standard World Health Organization (WHO) diagnostic criteria for osteoporosis (T-score of − 2.5 or lower at the lumbar spine, total hip, or femoral neck) are applied [53]. However, clinicians must interpret these results cautiously in patients with T2D, recognizing that significant fracture risk can exist even with T-scores in the osteopenic or normal range. Reflecting this, the ADA suggests considering antiresorptive therapy for patients with diabetes with a T-score ≤ −2.0 or those who have experienced fractures [51]. Vertebral Fracture Assessment (VFA), performed concurrently with DXA, should be considered on the basis of clinical indicators such as significant height loss (> 4 cm), self-reported prior vertebral fracture, older age (women ≥ 70 years, men ≥ 80 years), or long-term glucocorticoid use, to detect prevalent vertebral deformities, which are strong predictors of future fractures [52].

Standard laboratory investigations to exclude secondary causes of osteoporosis are also appropriate.

The potential inadequacy of current screening guidelines, largely mirroring those for the general population, is a concern. Given the elevated fracture risk that may manifest earlier or independent of traditional risk factors in diabetes, particularly T2D, a lower threshold for BMD testing or the formal incorporation of diabetes-specific risk factors (duration, glycemic control, complications) into screening algorithms warrants serious consideration to ensure timely identification and intervention.

4.2 Nonpharmacological Strategies

Lifestyle interventions form the foundation of bone health management for all older adults, including those with diabetes.

Adequate nutrition is crucial. Ensuring sufficient intake of calcium, typically recommended at 1000 mg/day for men aged 50–70 years and 1200 mg/day for women ≥ 51 years and men ≥ 71 years, is important, utilizing supplements if dietary intake is insufficient [53]. Vitamin D status should be assessed and optimized, as deficiency is common and exacerbates bone loss and muscle weakness. The Endocrine Society's 2024 guideline suggests empiric vitamin D supplementation for individuals aged 75 years and older owing to its potential to lower mortality risk [54, 55], aligning with the IOF recommendation of targeting serum 25-hydroxyvitamin D levels of at least 75 nmol/L (30 ng/mL) in older adults for optimal fall and fracture reduction [56]. It is worth noting that "For adults with high-risk prediabetes, in addition to lifestyle modification, we suggest empiric vitamin D supplementation to reduce the risk of progression to diabetes" is recommended in the Endocrine Society's 2024 guideline [57–59].

However, of note, there are concerns to setting the threshold to 30 ng/mL [60], and the 2024 Endocrine Society Guideline updated its recommendation to no longer endorse the target 25(OH)D level of 30 ng/mL (75 nmol/L) suggested in the previous guideline [54]. In general, a 25-hydroxyvitamin D level > 20 ng/mL is considered adequate for musculoskeletal outcomes [54, 61].

Adequate protein intake is also vital, particularly for frail older adults, to counteract sarcopenia and maintain muscle mass [8]. Some evidence suggests a Mediterranean dietary pattern may be beneficial for reducing fracture risk in T2D [8]. The Mediterranean diet has also emerged as a way to combat sarcopenia as well [62].

Regular physical activity, incorporating both weight-bearing (e.g., walking) and resistance exercises (strength training), is recommended to provide a beneficial mechanical load to the skeleton and prevent excessive bone loss in people with type 2 diabetes. This recommendation is based on evidence from a systematic review, including several studies conducted in older adults, supporting its relevance for older adults with diabetes [63, 64]. Importantly, recommendations for older adults emphasize not only aerobic and resistance training but also balance and flexibility exercises to reduce fall risk and address frailty. In older adults with diabetes—who are at increased risk of falls, particularly in the presence of peripheral neuropathy or functional impairment—The American Diabetes Association specifically recommends flexibility and balance training two to three times per week [65]. In addition, in a dedicated review focusing on diabetic elderly populations, Ferriolli et al. recommend combined aerobic and resistance training as the preferred modality, with resistance exercise being especially suitable for frail and vulnerable older adults, and with careful attention to hypoglycemia, orthostatic hypotension, and comorbidities [66]. Exercise

also plays a key role in improving glycemic control and facilitating weight management in T2D [64, 66]. Exercise programs must be tailored to the individual's capabilities and health status, especially considering potential limitations owing to diabetic complications or frailty [64].

Fall prevention strategies are one of the most critical non-pharmacological interventions for older adults with diabetes, given their markedly increased fall risk. This requires a multifactorial approach, including: regular medication review to minimize polypharmacy and identify drugs increasing fall risk (e.g., sedatives, agents causing orthostasis or hypoglycemia); screening for and managing orthostatic hypotension; optimizing vision through regular eye exams and appropriate corrective lenses; assessing and managing peripheral neuropathy, potentially including protective footwear; conducting home safety evaluations to remove hazards; and recommending specific exercise programs incorporating balance, gait, and strength training, often guided by physical therapy. The high prevalence of diabetes-specific fall risk factors underscores the paramount importance of these measures.

Finally, general lifestyle advice includes smoking cessation and avoiding excessive alcohol consumption, both of which negatively impact bone health [8].

4.3 Glycemic Management Considerations for Bone Health

Optimizing glycemic control in older adults with diabetes involves navigating a careful balance between mitigating the long-term detrimental effects of chronic hyperglycemia on bone quality and preventing the acute risks associated with hypoglycemia, particularly fall-related fractures [1]. This necessitates individualized glycemic targets and thoughtful medication selection.

Guidelines consistently recommend tailoring HbA1c goals on the basis of the older adult's overall health status, functional and cognitive capacity, presence of comorbidities, life expectancy, and risk of adverse events such as hypoglycemia [67]. For relatively healthy older adults with good functional status and few comorbidities, stricter targets (e.g., HbA1c < 7.0–7.5%) may be appropriate to reduce microvascular complication risk. However, for individuals who are frail and have multiple complex comorbidities, cognitive impairment, or limited life expectancy, more relaxed targets (e.g., HbA1c < 8.0–8.5%) are advised to prioritize safety and avoid the harms of intensive therapy [68]. Overtreatment and the pursuit of overly stringent glycemic goals should be actively avoided in vulnerable older populations [69]. One study suggested that an HbA1c range of 6.5–6.9% was associated with the lowest fracture risk in older patients with diabetes, with risk increasing at both lower and higher levels [69].

Medication choice plays a critical role in achieving this balance. Agents with a low intrinsic risk of hypoglycemia are strongly preferred, particularly in patients with known risk factors for hypoglycemia (e.g., advanced age, renal impairment, erratic eating habits, cognitive impairment) [67]. This favors the use of metformin, dipeptidyl peptidase-4 inhibitors (DPP-4i), glucagon-like peptide-1 receptor agonists (GLP-1 RAs), and sodium-glucose co-transporter-2 inhibitors (SGLT-2i) over insulin and sulfonylureas [70]. Insulin secretagogues (sulfonylureas, meglitinides) should be used with significant caution, and long-acting sulfonylureas such as glyburide are generally discouraged in older adults owing to the prolonged risk of hypoglycemia. [71]. Insulin therapy, while often necessary, requires careful patient selection, education, and strategies to minimize hypoglycemia risk, such as using analogs over older formulations and simplifying regimens where possible [71]. Continuous glucose monitoring (CGM) can be a valuable tool for detecting and preventing hypoglycemia, particularly in patients treated with insulin [22]. However, cost and related insurance regulations may be a barrier in this road.

Furthermore, medication selection should also consider potential cardiorenal benefits, with GLP-1 RAs and SGLT-2i recommended for patients with established or high risk of atherosclerotic cardiovascular disease, heart failure, or CKD, irrespective of baseline HbA1c [72].

However, weight loss effects that may possibly cause skeletal muscle loss and sarcopenia, predominantly parenteral route in most of the GLP-1 agonists or urinary incontinence with SGLT-2i, which may increase fall risk, are barriers to be considered along with their higher costs [73].

The potential impact of the chosen antidiabetic agent on bone health itself (Sect. 5) adds another layer to this complex decision-making process.

5 Effects of Antidiabetic Medications on Skeletal Health

Beyond their primary glucose-lowering effects, antidiabetic medications can exert direct or indirect influences on bone metabolism and fracture risk. Understanding these skeletal effects is crucial when selecting therapy for older adults with diabetes, who are already at heightened risk for fractures. The available agents demonstrate a spectrum of effects, from clearly detrimental to neutral or potentially beneficial, although evidence quality varies and is often derived from observational studies or post hoc analyses of trials not primarily designed to assess skeletal outcomes [74]. These effects must be weighed alongside glycemic efficacy, hypoglycemia risk, impact on comorbidities (cardiovascular, renal), side effect profile, cost, and patient preferences. Table 2 presents a summary overview.

5.1 Metformin

Metformin remains the cornerstone of T2D therapy [71]. Preclinical studies suggest potential beneficial bone effects through activation of AMP-activated protein kinase (AMPK), promoting osteoblast differentiation and inhibiting cellular senescence and inflammation [75].

Clinical evidence regarding its impact on BMD and bone turnover markers is mixed, with some studies showing neutral effects or even potential inhibition of mineralization at high concentrations, while others, including Mendelian randomization studies, suggest a positive impact on BMD at the lumbar spine, femoral neck, and heel [76]. Similarly, data on fracture risk are conflicting. While some observational studies and Mendelian randomization analyses point toward a reduced risk [76], several recent meta-analyses have failed to demonstrate a statistically significant association between metformin use and a lower risk of overall or hip fractures. Overall, metformin is generally considered to have a neutral to possibly mildly beneficial skeletal profile [77].

Its established efficacy, low cost, low hypoglycemia risk, and potential cardiovascular benefits support its continued use as first-line therapy, with appropriate monitoring for gastrointestinal side effects and vitamin B12 levels, and caution in significant renal impairment (not recommended when estimated glomerular filtration rate [eGFR] is < 30 mL/min) [71, 78]. Other contraindications, i.e., cirrhosis and pulmonary disease with hypoxia, must also be considered. In addition, in older adults prone to malnutrition, it can cause weight loss and should not be prioritized [73, 79–82].

5.2 Sulfonylureas (SUs) and Meglitinides

These insulin secretagogues primarily act by stimulating insulin release from pancreatic β cells. Direct effects on bone metabolism are largely unknown. The main concern regarding their use in older adults relates to their significant risk of inducing hypoglycemia [71]. This hypoglycemia risk is strongly implicated as the primary driver for the observed association between SU use and increased fracture risk [83]. Meta-analyses consistently demonstrate that sulfonylurea (SU) users have a higher risk of hip fractures compared with nonusers, with a pooled hazard ratio (HR) of 1.175 [84]. Compared with other agents, SUs confer a higher fracture risk than metformin but a lower risk than insulin [83]. Owing to the high risk of hypoglycemia and consequent falls, SUs, especially long-acting agents such as glyburide, should be used with extreme caution in older adults, if at all [71, 73, 78].

5.3 Thiazolidinediones (TZDs)

TZDs (pioglitazone, rosiglitazone) exert their glucose-lowering effects by activating peroxisome proliferator-activated receptor gamma (PPARγ). Unfortunately, PPARγ activation in mesenchymal stem cells shunts differentiation away from the osteoblast lineage toward adipogenesis, thereby impairing bone formation [85]. This mechanism underlies the consistent and robust evidence linking TZD use to accelerated bone loss and a significantly increased risk of fractures [77]. This detrimental effect has been observed in postmenopausal women [77]. Although TZDs carry a low risk of hypoglycemia, their negative skeletal impact, coupled with risks of fluid retention, heart failure, and potential macular edema, makes them a poor choice for most older adults, especially those with preexisting osteoporosis or high fracture risk [73, 85]. While pioglitazone may confer certain cardiovascular benefits, these must be carefully weighed against its skeletal adverse effects, particularly the increased fracture risk in women. Therefore, treatment decisions should prioritize an individualized balance between cardiovascular and bone health outcomes [86].

5.4 Dipeptidyl Peptidase-4 Inhibitors (DPP-4i)

DPP-4i (e.g., sitagliptin, saxagliptin, linagliptin, alogliptin) enhance endogenous levels of incretin hormones GLP-1 and GIP. Preclinical studies suggested potential bone benefits mediated by these incretins [87]. However, clinical evidence regarding fracture risk has been inconsistent. An early meta-analysis suggested a possible protective effect [87]. A meta-analysis of randomized controlled trials suggested a potential reduction in fracture risk with DPP-4 inhibitor treatment compared with placebo or other antidiabetic agent [85]. One network meta-analysis raised a potential signal for increased risk with trelagliptin, but this requires confirmation [88]. Overall, the class is currently considered bone-neutral [85]. DPP-4 inhibitors offer the advantage of a low hypoglycemia risk and good tolerability but generally lack the significant cardiovascular and renal benefits seen with GLP-1 RAs and SGLT-2i [71].

5.5 GLP-1 Receptor Agonists (GLP-1 RAs)

GLP-1 RAs (e.g., liraglutide, semaglutide, dulaglutide, exenatide) mimic the action of endogenous GLP-1. GLP-1 receptors have been identified on osteoblasts and osteocytes, and preclinical studies suggest potential mechanisms for bone benefit, including promoting osteoblast differentiation and inhibiting bone resorption [89]. Human data on fracture risk are mixed. In a network meta-analysis comparing the fracture risk probabilities of different GLP-1 receptor agonists, exenatide was found to have the lowest risk (0.07‰),

Table 2 Bone health implications of antidiabetic medications in older adults

Class	Proposed mechanism of bone effect (if known)	Effect on BMD (evidence summary)	Effect on bone turnover markers (evidence summary)	Effect on fracture risk (evidence summary and pooled RR/HR)	Hypoglycemia risk	Key considerations in older adults/diabetes
Metformin	AMPK activation; ↑ osteoblastogenesis; ↓ inflammation/senescence [59]	Neutral or potentially positive (MR suggests ↑LS/FN/Heel BMD)	Variable; may ↑ formation or be neutral	Generally neutral (meta-analyses RR ~0.9–1.0) [68]; MR suggests ↓ risk [60]; possibly beneficial [58]	Low	First-line; GI side effects; B12 monitoring; renal caution [55]
Sulfonylureas (SUs)/meglitinides	Indirect via hypoglycemia/falls; direct effects unclear	Likely neutral	Unclear	Increased (meta-analyses HR: 1.14 overall versus nonusers; ↑ versus metformin; ↓ versus insulin) [60]; primarily via falls [67]	High	Avoid long-acting SUs (glyburide); use cautiously owing to fall risk [55]
Thiazolidinediones (TZDs)	PPARγ activation; ↑ adipogenesis; ↓ osteoblastogenesis [58]	Decreased [61]	Decreased formation	Increased [61]	Low	Avoid in patients with fracture risk, osteoporosis, HF; edema risk [58]
DPP-4 inhibitors	↑ Endogenous GLP-1/GIP; potential incretin effects on bone [71]	Neutral	Neutral	Generally neutral (meta-analyses RR ~0.8–1.6 versus placebo/active) [58]; early meta-analysis suggested ↓ risk [71]; trelagliptin outlier? [72]	Low	Well-tolerated; lack major CV/renal benefits [55]
GLP-1 receptor agonists (GLP-1 RAs)	GLP-1R on bone cells; ↑ formation?; ↓ resorption?; Wnt signaling? [73]	Neutral or ↓ with significant weight loss (Semaglutide study) [75]	Variable; ↑ formation and ↓ resorption in animals; ↑ CTX, neutral P1NP with semaglutide [75]	Neutral or decreased (meta-analyses RR ~0.7 versus controls, especially > 52 weeks, Lira/Lixi/Albi) [58]	Low	CV benefits; weight loss; GI side effects; monitor bone with major weight loss [55]
SGLT-2 inhibitors	Indirect via Ca/Phos/PTH/VitD changes?; weight loss	Generally neutral [78]	Variable/transient; ↑ CTX reported with Cana/Ertu initially; meta-analysis ↑ PTH/CTX, [78]	Generally neutral (multiple meta-analyses and large cohort studies RR ~0.9–1.2 versus placebo/DPP-4i/GLP-1 RAs) [61]; initial Cana signal not confirmed class-wide [56]	Low	CV and renal benefits; GU infection risk; dehydration/hypotension risk (falls); DKA risk [78]
Insulin	Physiological anabolic effect; clinical use confounded	Variable; may accelerate loss at FN	Unclear in clinical setting	Increased (observational studies/meta-analyses RR ~1.2–1.4 versus OADs) [1]; likely due to confounding (severity/duration) and hypoglycemia/falls [1]	High	Essential for T1D/advanced T2D; requires skills/education; minimize hypoglycemia

AMP adenosine monophosphate, *albi* albiglutide, *AMPK* AMP-activated protein kinase, *BMD* bone mineral density, *Ca* calcium, *cana* canagliflozin, *CTx* C-terminal telopeptide of type I collagen, *CV* cardiovascular, *DKA* diabetic ketoacidosis, *ertu* ertugliflozin, *DPP-4* dipeptidyl peptidase-4, *FN* femoral neck, *GI* gastrointestinal, *GLP-1/GIP* glucagon-like peptide-1/glucose-dependent insulinotropic polypeptide, *GLP-1 RAs* glucagon-like peptide-1 receptor agonists, *GU* genitourinary, *HF* heart failure, *HR* hazard ratio, *lira* liraglutide, *lixi* lixiglutide, *LS* lumbar spine, *MR* Mendelian randomization, *OAD* oral antidiabetics, *P* phosphorus, *P1NP* procollagen type 1 N-terminal propeptide, *PPAR-γ* peroxisome proliferator-activated receptor gamma, *PTH* parathyroid hormone, *RR* relative risk, *SGLT-2* sodium-glucose co-transporter-2, *T1D* type 1 diabetes, *T2D* type 2 diabetes, *VitD* vitamin D

followed by dulaglutide (1.04%), liraglutide (1.39%), albiglutide (5.61%), lixisenatide (8.07%), and semaglutide (18.72%). These findings suggest a potential difference in skeletal safety profiles among individual agents [90]. Importantly, it should be noted that studies conducted in patients with type 2 diabetes typically use antidiabetic doses of GLP-1 receptor agonists, whereas trials in individuals with obesity employ substantially higher doses for weight-loss indications, which may partly explain the heterogeneity in reported skeletal outcomes.

However, a recent randomized trial investigating semaglutide, one of the GLP-1 RAs in adults at increased fracture risk (though not exclusively diabetic) found no increase in bone formation markers (P1NP) but did observe an increase in the resorption marker CTX and modest decreases in hip and spine BMD over 52 weeks [91]. This was hypothesized to be related to the significant weight loss induced by semaglutide [91]. Currently, the class is generally viewed as having neutral to potentially favorable effects on fracture risk [85]. Key advantages include low hypoglycemia risk, significant weight loss potential, and proven cardiovascular benefits [71]. Potential downsides include gastrointestinal side effects and the need for injection (except for oral semaglutide). The impact of substantial GLP-1 RA-induced weight loss on bone health warrants further investigation and monitoring [91].

5.6 SGLT-2 Inhibitors

SGLT-2i (e.g., empagliflozin, canagliflozin, dapagliflozin, ertugliflozin) lower glucose by promoting urinary glucose excretion. Initial concerns about potential adverse skeletal effects arose from the CANVAS trial, which reported an increased fracture risk with canagliflozin [92]. Proposed mechanisms included potential alterations in calcium and phosphate homeostasis (transient increases in serum phosphate, PTH, FGF23, and decreases in 1,25-dihydroxyvitamin D reported in some early studies, particularly with canagliflozin) and effects related to volume depletion or weight loss [85]. However, subsequent large-scale cardiovascular outcome trials for other agents in the class (empagliflozin, dapagliflozin) did not replicate this finding [93]. Numerous meta-analyses pooling data from extensive randomized controlled trial (RCT) programs, as well as large observational cohort studies comparing SGLT-2i initiation with DPP-4i or GLP-1 RAs initiation in real-world settings (including older adults and those with CKD), have consistently found no overall increased risk of fractures associated with the SGLT-2i class [77]. Most studies also show no clinically significant long-term effects on BMD or bone turnover markers, although some transient changes or minor effects on certain markers (e.g., increased CTX) have been noted in specific studies or meta-analyses [94]. Therefore, the current consensus is that SGLT-2i as a class are generally bone-neutral. Their significant benefits in reducing cardiovascular events, heart failure hospitalizations, and progression of CKD make them valuable therapeutic options, particularly in patients with these comorbidities [71]. Potential risks relevant to older adults include genitourinary infections, and a potential for volume depletion leading to orthostatic hypotension and falls, which requires careful monitoring [73, 94]. Moreover, in older patients—particularly in the setting of dehydration or acute infection—SGLT-2 inhibitors may increase the risk of metabolic acidosis, most notably euglycemic diabetic ketoacidosis, underscoring the importance of careful patient selection and temporary drug interruption during acute illness.

5.7 Insulin

While endogenous insulin plays an anabolic role in bone physiology [4], the clinical use of exogenous insulin therapy is paradoxically associated with an increased risk of fractures in numerous observational studies and meta-analyses [1]. Pooled risk ratios suggest an approximate 20–40% increase in fracture risk compared with oral antidiabetic drug users [95]. This association is complex and likely driven primarily by confounding factors rather than a direct adverse effect of insulin on bone. Insulin use typically signifies longer diabetes duration, greater disease severity, poorer glycemic control, and a higher burden of diabetic complications—all independent risk factors for fracture. Critically, insulin therapy carries the highest risk of severe hypoglycemia among all antidiabetic treatments, substantially increasing the risk of falls [96]. Some longitudinal data also suggest that insulin initiation may be associated with accelerated BMD loss at the femoral neck [97]. While essential for survival in T1D and often necessary for achieving glycemic control in advanced T2D, insulin therapy requires careful management in older adults, focusing on individualized goals, patient education on hypoglycemia prevention and management, and potentially simplifying regimens to minimize risk [71, 73, 78].

6 Osteoporosis Pharmacotherapy in Older Adults with Diabetes

While specific guidelines for treating osteoporosis in patients with diabetes are lacking [22], the overarching goal remains fracture prevention. Treatment decisions should be guided by general osteoporosis management principles, including risk stratification, while considering the unique aspects of diabetes [22]. Evidence regarding the efficacy and safety of specific anti-osteoporosis medications in populations with diabetes is often derived from subgroup analyses of

pivotal trials, post hoc analyses, or observational studies, rather than dedicated prospective RCTs [22]. Importantly, although several post hoc analyses included substantial numbers of older participants, most pivotal trials were not specifically designed to investigate cohorts of older adults with diabetes, and age-stratified analyses in this subgroup remain limited. Nevertheless, available data suggest that current therapies are generally effective in diabetic individuals, although nuances related to the underlying pathophysiology and potential drug interactions warrant consideration. Table 3 summarizes the evidence for major osteoporosis drug classes.

6.1 Antiresorptive Therapies

Antiresorptive agents, which reduce bone breakdown by inhibiting osteoclast activity, are the most commonly used treatments for osteoporosis.

Bisphosphonates: This class includes oral agents (alendronate, risedronate, ibandronate) and an intravenous agent (zoledronic acid). Post hoc analyses of pivotal fracture trials (e.g., FIT with alendronate, HORIZON-PFT with zoledronic acid) and observational studies have suggested that bisphosphonates provide similar improvements in BMD and reductions in nonvertebral fracture risk in older women with T2D as they do in women without diabetes [22]. A meta-analysis focusing on diabetic osteoporosis confirmed significant improvements in BMD at various sites with bisphosphonate treatment [98], and one study showed similar efficacy for monthly oral ibandronate in postmenopausal women with and without T2D [99]. Bisphosphonates are generally considered effective and safe in older adults [100]. However, their use requires careful consideration of renal function, as they are renally excreted and typically contraindicated or require dose adjustment in moderate-to-severe CKD—a common comorbidity in diabetes [100]. Gastrointestinal intolerance can be an issue with oral formulations. While concerns exist about potentially exacerbating the underlying low bone turnover state in T2D, studies have not shown an associated increase in fracture risk, particularly if glycemic control is reasonable [22]. The risks of rare long-term adverse events, osteonecrosis of the jaw (ONJ), and atypical femoral fractures (AFF), necessitate consideration of drug holidays after several years of use in appropriate patients [100].

Denosumab: This monoclonal antibody against RANKL is a potent antiresorptive administered via subcutaneous injection every 6 months. A post hoc analysis of the FREEDOM trial and its extension found that denosumab increased BMD and reduced vertebral fractures in women with T2D, although one analysis suggested a possible increase in nonvertebral fracture risk in this subgroup [22]. Other analyses and real-world data generally support its efficacy in patients with diabetes [101]. Intriguingly, some recent large cohort studies and meta-analyses suggest denosumab use may be associated with a lower risk of developing incident T2D compared with bisphosphonates, and potentially improve glycemic parameters, especially in those with impaired glucose tolerance [102, 103]. Denosumab offers sustained BMD gains over at least 10 years [101]. Key safety considerations include the risk of hypocalcemia (requiring adequate calcium and vitamin D status and monitoring, especially in CKD), and rare risks of ONJ and AFF [101]. A critical aspect of denosumab therapy is the rapid reversal of its effects and potential for rebound increase in bone turnover and multiple vertebral fractures upon discontinuation; therefore, transitioning to another antiresorptive (typically a bisphosphonate) is essential if denosumab is stopped [101]. It can generally be used in patients with impaired renal function, albeit with increased vigilance for hypocalcemia [101].

6.2 Anabolic Therapies

Anabolic agents stimulate new bone formation by activating osteoblasts, offering a different therapeutic approach, particularly relevant for conditions characterized by low bone turnover.

Teriparatide: A recombinant form of human parathyroid hormone (PTH 1-34), administered via daily subcutaneous injection. Post hoc analyses of the DANCE observational study and other data suggest that teriparatide produces similar increases in BMD and reductions in clinical fracture rates in patients with T2D compared with those without diabetes [22]. Given the low bone turnover state often seen in T2D, teriparatide theoretically offers an advantage by directly stimulating bone formation [22]. It is generally well tolerated, with potential side effects including transient hypercalcemia [104]. Treatment duration is typically limited to 18–24 months, after which therapy should be followed by an antiresorptive agent to maintain bone gains.

Abaloparatide: A synthetic analog of PTH-related protein (PTHrP), also administered via daily subcutaneous injection. A post hoc analysis of the ACTIVE trial demonstrated significant improvements in BMD at the hip, femoral neck, and spine, as well as fewer nonvertebral fractures compared with placebo, in postmenopausal women with T2D [22]. Some evidence, including comparative trials and retrospective claims data, suggests abaloparatide may produce greater BMD gains at hip sites and potentially lower rates of hip and nonvertebral fractures compared with teriparatid [105, 106]. Safety considerations include potential transient hypercalcemia, injection site reactions, and orthostatic hypotension or palpitations shortly after injection [107]. Similar to teriparatide, treatment duration is limited, and follow-on antiresorptive therapy is required.

Table 3 Evidence summary for osteoporosis medications in older adults with diabetes

Medication class	Mechanism of action	Evidence for efficacy in diabetes (BMD, fractures)	Key safety considerations in diabetes/older adults
Bisphosphonates (oral/IV)	Inhibit osteoclast activity/resorption	Similar BMD ↑ and fracture ↓ versus nondiabetics (post hoc/obs.) [21]; meta-analysis shows BMD ↑ [82]	Renal dosing crucial; GI issues (oral); ONJ/AFF risk (long-term); low turnover concern (theoretical) [21]
Denosumab	RANKL inhibitor; inhibits osteoclast formation/function/survival	Similar BMD ↑ and Vert Fx ↓ versus nondiabetics (post hoc) [21]; NVF data mixed (↑ risk in one analysis) [21]; potential ↓ incident T2D risk [86]; may improve glucose parameters [87]	Hypocalcemia risk (monitor Ca/VitD); ONJ/AFF risk; rebound loss/fractures on cessation (needs transition); usable in CKD (monitor) [85]
Teriparatide (PTH 1-34)	Anabolic; stimulates osteoblast function/bone formation	Similar BMD ↑ and fracture ↓ versus nondiabetics (post hoc/obs.) [21]; theoretical benefit in low turnover T2D [21]	Transient hypercalcemia; daily injection; limited to 2 years of use; follow with antiresorptive
Abaloparatide (PTHrP analog)	Anabolic; selective PTH1R activation	Significant BMD ↑ and ↓ NVF versus placebo in T2D subgroup (post hoc ACTIVE) [21]; may ↑ BMD > teriparatide at hip [89]; ↓ hip/NVF versus teriparatide (claims data) [90]	Transient hypercalcemia; injection reactions; palpitations; limited to 2 years of use (trials of fracture efficacy lasted only 18–21 months); follow with antiresorptive [91]
Romosozumab (anti-sclerostin Ab)	Dual action: ↑ formation, ↓ resorption	Potent BMD ↑ and fracture ↓ versus placebo/alendronate (general population) [96]; limited data in diabetes [93]; preclinical T2D data promising [21]	CV safety signal (↑ MI/stroke risk versus alendronate in ARCH trial); contraindicated post-MI/stroke; hypocalcemia risk; ONJ/AFF risk; limited to 12 months of use; follow with antiresorptive [96]

Ab antibody, *AFF* atypical femoral fracture, *BMD* bone mineral density, *Ca* calcium, *CKD* chronic kidney disease, *Fx* fracture, *GI* gastrointestinal, *IV* intravenous, *MI* myocardial infarction, *NVF* nonvertebral fracture, *obs* observational studies, *ONJ* osteonecrosis of the jaw, *PTH* parathyroid hormone, *PTHrP* PTH-related peptide, *PTH1R* parathyroid hormone-1 receptor, *T2D* type 2 diabetes, *VitD* vitamin D

6.3 Dual-Acting Therapy

Romosozumab: A monoclonal antibody that inhibits sclerostin, resulting in a dual effect of rapidly increasing bone formation while simultaneously decreasing bone resorption [108]. It produces substantial and rapid increases in BMD and significant reductions in vertebral, nonvertebral, and hip fractures compared with placebo and alendronate in the general postmenopausal population [108]. Data specifically evaluating its efficacy in patients with diabetes are currently limited [109], although preclinical studies in diabetic animal models are encouraging [22]. A major consideration with romosozumab is a potential cardiovascular safety signal. An imbalance in serious adjudicated cardiovascular events (myocardial infarction, stroke) was observed in the ARCH trial comparing romosozumab to alendronate, leading to a boxed warning and contraindication in patients with a history of myocardial infarction (MI) or stroke within the preceding year [108]. Some authors also consider the presence of a high cardiovascular event risk as a contraindication for romosozumab. As such, while meta-analyses have yielded mixed results regarding the overall cardiovascular (CV) risk, caution is warranted, particularly in patients with high cardiovascular risk [110]. Other potential adverse effects include hypocalcemia, injection site reactions, and rare risks of ONJ and AFF [111]. Romosozumab is administered as monthly subcutaneous injections for a maximum of 12 months, after which treatment must be transitioned to an antiresorptive agent to consolidate gains [112].

6.4 Treatment Selection Considerations in Diabetes

Selecting the optimal osteoporosis therapy for an older adult with diabetes requires integrating general principles of goal-directed treatment with diabetes-specific considerations. Risk stratification based on fracture history (especially recent or severe fractures), BMD levels, and clinical risk factors, including those related to diabetes, is crucial [113].

For patients deemed to be at very high risk (e.g., recent major osteoporotic fracture, multiple fractures, very low T-scores), guidelines increasingly recommend initiating therapy with an anabolic agent (teriparatide or abaloparatide) or, if cardiovascular risk allows, romosozumab, to achieve rapid and substantial fracture risk reduction [113]. This approach aligns theoretically with the low bone turnover pathophysiology often present in T2D, where stimulating formation may be particularly beneficial [22]. However, this theoretical rationale needs confirmation through direct comparative studies in populations with diabetes. For patients at high, but not very high, risk, potent antiresorptives such as bisphosphonates (especially intravenous [IV] zoledronic acid) or denosumab remain appropriate and effective first-line choices.

Comorbidities common in older patients with diabetes heavily influence treatment choice. Renal function must be assessed before initiating bisphosphonates, potentially favoring denosumab or anabolic agents in patients with significant CKD. A recent study by our group also revealed predilection of denosumab and then anabolics in patients with CKD [114].

Cardiovascular history is a key determinant when considering romosozumab. Patient preferences regarding administration route (oral, subcutaneous, intravenous) and frequency also play a role. Regardless of the initial agent chosen, the importance of sequential therapy—following anabolic or romosozumab treatment with an antiresorptive—must be emphasized to maintain the accrued benefits. While awaiting more definitive diabetes-specific data, clinicians should leverage current goal-directed osteoporosis treatment paradigms, potentially prioritizing anabolic therapies earlier for very high-risk patients with T2D, while always performing a thorough individual risk–benefit assessment.

7 Emerging Therapies and Future Directions

The management of bone fragility in diabetes is an evolving field, with ongoing research aimed at elucidating pathophysiology, improving diagnostics, and developing more targeted therapies.

Several novel therapeutic targets are emerging on the basis of our understanding of the underlying mechanisms. Strategies aimed at inhibiting the formation or accumulation of AGEs or blocking the RAGE signaling pathway could potentially mitigate AGE-induced bone damage [20]. Modulating key signaling pathways involved in bone remodeling, such as the Wnt/β-catenin pathway (potentially influenced by GLP-1 RAs or sclerostin inhibitors) or the mammalian target of rapamycin (mTOR) pathway, represents another avenue [115]. Inhibitors of glycogen synthase kinase 3 beta (GSK3β) and therapies based on exosomes (extracellular vesicles involved in cell-to-cell communication) are also under investigation [116]. Furthermore, addressing chronic inflammation and oxidative stress, perhaps through targeted anti-inflammatory or antioxidant therapies, may hold promise [116]. Inhibition of myostatin, a negative regulator of muscle growth, has shown benefits for both muscle and bone in preclinical diabetic models, suggesting another potential therapeutic approach [117].

Improvements in diagnostic tools are urgently needed to better assess bone quality noninvasively and refine risk prediction beyond BMD, standard FRAX, and in some aspects, FRAXplus. Advanced imaging techniques such as HR-pQCT offer insights into microarchitecture and material

properties but require further validation and wider accessibility [9]. The identification and validation of reliable biomarkers are crucial. This could include specific AGEs measured in serum or urine, bone turnover markers adjusted for the altered turnover state in diabetes, and circulating levels of regulators such as sclerostin [9].

Significant research gaps remain. There is a critical need for prospective, randomized controlled trials specifically designed to evaluate the efficacy and long-term safety of existing and emerging osteoporosis therapies within diverse populations of patients with T1D and T2D. Head-to-head comparisons between different drug classes within the diabetic context are also lacking. Further longitudinal studies are required to clarify the long-term skeletal impact of newer antidiabetic medications, particularly GLP-1 RAs and SGLT-2i, considering factors such as weight change. A deeper understanding of the complex interplay between diabetes, obesity, sarcopenia, frailty, and bone health is needed to develop integrated management strategies. Finally, the development and validation of accurate, easy-to-use, diabetes-specific fracture risk prediction tools are essential for routine clinical practice [118]. Addressing these gaps through dedicated research within cohorts with diabetes is paramount to move beyond extrapolation from general population data and establish truly evidence-based, tailored management paradigms for diabetic bone disease.

In this context, future research and therapeutic strategies must specifically address the needs of older adults with diabetes, who represent the highest-risk group for fractures and adverse outcomes. In this population, bone fragility frequently coexists with frailty, sarcopenia, multimorbidity, cognitive impairment, and an increased risk of falls, necessitating an integrated geriatric approach rather than a single-disease model. Emerging therapies should therefore be evaluated not only for their skeletal efficacy but also for their impact on muscle function, physical performance, fall risk, cardiovascular safety, and treatment burden in frail older patients with diabetes. Dedicated trials focusing on older adults living with frailty and diabetes are essential to develop truly individualized and clinically meaningful management strategies.

8 Conclusions

Bone fragility represents a significant and often underappreciated complication of both T1D and T2D in older adults, contributing substantially to fracture risk, morbidity, and mortality. The underlying pathophysiology is complex and differs between diabetes types, with T1D primarily characterized by reduced bone mass and T2D by impaired bone quality despite often normal or high BMD. This distinction, particularly the "diabetic paradox" in T2D, poses significant challenges for accurate risk assessment using standard tools such as DXA, FRAX, and even FRAXplus, which frequently underestimate the true fracture probability.

Effective management demands a holistic, individualized approach that integrates geriatric principles. Key components include comprehensive risk assessment incorporating diabetes-specific factors (duration, glycemic control, complications) and fall risk evaluation, alongside potential adjustments to standard prediction tools. Lifestyle interventions focusing on adequate nutrition (calcium, vitamin D, protein), appropriate weight-bearing and resistance exercise, and rigorous fall prevention strategies are fundamental. Glycemic management must balance the long-term goal of minimizing hyperglycemia-related bone damage with the immediate need to prevent hypoglycemia-induced falls, necessitating personalized HbA1c targets and preferential use of antidiabetic agents with low hypoglycemia risk. The choice of antidiabetic medication should also consider direct skeletal effects, avoiding agents known to be detrimental (TZDs) and favoring those with neutral or potentially beneficial profiles (metformin, DPP-4i, GLP-1 RAs, SGLT-2i), while also weighing cardiovascular and renal benefits with holistic evaluation of each patient on a case by case basis.

When osteoporosis pharmacotherapy is indicated, current evidence, though limited primarily to post hoc analyses and observational studies, suggests that standard treatments (bisphosphonates, denosumab, anabolic agents) are effective in patients with diabetes. However, treatment decisions should apply goal-directed principles, potentially favoring anabolic agents earlier in very high-risk patients with T2D, owing to the underlying low bone turnover state, while carefully considering comorbidities such as renal impairment and cardiovascular risk.

Significant research is needed to fill existing knowledge gaps, particularly through prospective trials of osteoporosis therapies specifically in populations with diabetes, development of better diagnostic tools for bone quality, and validation of diabetes-specific risk prediction models. Until then, clinicians must maintain a high index of suspicion for bone fragility in their older patients with diabetes, employ a comprehensive assessment strategy, and implement personalized, multifactorial interventions to mitigate fracture risk and improve patient outcomes.

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Declarations

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