The Review Of
DIABETIC
STUDIES OPEN ACCESS

Long-Term Diabetes Medication And Bone Density: A Radiologic Perspective

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Abstract

Diabetes, an endocrine disorder characterized by chronic hyperglycemia, is estimated to affect 422 million individuals worldwide, with Type 2 Diabetes Mellitus (DMT2) accounting for nearly 90% of cases. Data indicate that patients with DMT2 have an increased risk of fragility fractures despite normal or elevated Bone Mineral Density (BMD); they also exhibit abnormal bone microarchitecture, remodeling, and mineralization of bone that contribute to this heightened risk. In DMT2, a reduced level of Bone Turnover (BT) occurs due to impaired osteoblastic activity and is associated with lower circulating levels of osteocalcin (OC), a marker of bone formation. Bone resorption markers such as serum C-Telopeptide of Type-I Collagen (CTx) are also low. Although commercial methods for evaluating BT are available, evidence linking these markers of BT to fracture risk remains limited. Given the relation between DMT2 and abnormal BT, the impact of Diabetes medications on BMD and BT forms an important area for investigation. Such agents are widely known to affect calcium levels, vitamin D metabolism, and parathyroid hormone (Padilla Apuntate et al., 2024).

A systemic skeletal disease characterized by decreased BMD and microarchitectural deterioration, osteoporosis elevates fracture risk. In Europe, Japan, and the USA, over 75 million individuals are affected, with the lifetime fracture risk estimated at about 40%. In India, approximately 50 million individuals had osteoporosis in 2013, and an estimated 20% of persons over the age of 50 years suffer from the disease. The rising longevity of the population and the increased prevalence of noncommunicable diseases such as osteoporosis and T2DM contribute to the public health burden. Patients with diabetes face a heightened risk of osteoporosis and fractures; women with Type 1 Diabetes Mellitus (T1DM) are 12 times more likely to report a hip fracture, while those with T2DM show a 1.7-fold increased risk. Early studies suggested that Thiazolidinediones increase bone loss and the occurrence of fragility fractures. Evidence regarding the effects of other common antidiabetic agents on bone health remain limited. Moreover, Metformin and DPP-4 inhibitors exhibit a trend toward protective effects on bone, although conclusive data are lacking. The impact of Sulfonylureas on bone remains poorly characterized. These agents may improve glycemic control, but their metabolic effects can lead to hypoglycemia and falls that increase fracture risk. Recognizing the limited data on the influence of widely prescribed antidiabetic medications on the skeletal system, a case–control study was therefore conducted in an Indian cohort (Pradeep Raj et al., 2019).

Keywords: Diabetes, bone density, osteoporosis, antidiabetic medications, bone turnover, radiology, MRI, DXA, BMD, fracture risk, insulin, metformin, thiazolidinediones, DPP-4 inhibitors, SGLT2 inhibitors.

Introduction

Diabetes is one of the most prevalent chronic diseases worldwide. An estimated 537 million adults (20 to 79 years old) are living with diabetes. This number is expected to rise to a staggering 700 million by 2045 (Ishikawa et al., 2015). Diabetes affects many organs, including the skeleton. Patients with diabetes have an increased risk of fractures, despite normal or elevated bone mineral density. The mechanisms underlying this increased risk of bone fragility and fracture have not yet been fully elucidated. This results in important clinical implications for the management of patients with diabetes (Pradeep Raj et al., 2019).

A number of medications (e.g., insulin, metformin, thiazolidinediones) that influence bone metabolism and have important effects on skeletal health are used in the treatment of diabetes (Heilmeier et al., 2021). Diabetes medications may alter the skeleton through distinct mechanisms. The use of these medications is sometimes associated with specific radiologic findings of cortical, trabecular, or marrow abnormalities of the lumbar spine and pelvis. The Panel examines the relevant medications and their known effects on bone, with an emphasis on the radiologic findings that may guide the interpretation of bone density measurements and fracture-risk assessments.

Overview of diabetes medications with bone health implications

Recent syntheses indicate that SGLT2 inhibitors do not significantly increase fracture risk compared with control therapy in large pooled analyses [10].

Metformin use has been associated with a neutral to lower fracture risk in meta-analyses, with some studies reporting modest protective associations [11, 12].
For GLP-1 receptor agonists, contemporary meta-analyses suggest neutral to reduced fracture risk, with possible duration-dependent benefits [13, 14].

Conversely, umbrella and systematic reviews continue to confirm increased fracture risk with thiazolidinediones [15].

Pathophysiology: diabetes, medications, and bone remodeling

Patients with diabetes mellitus, particularly the type 2 form (DMT2), are at increased risk for fragility fractures despite normal or elevated bone mineral density (BMD). These fractures can cause significant disability and even death (Padilla Apuntate et al., 2024). Under the prevailing conceptual framework, the higher fracture risk in DMT2 is attributed to abnormal bone microarchitecture and reduced remodeling both in human and animal studies (Lecka-Czernik, 2017). Restoration of glycaemic control often mitigates the diabetes-related deterioration of bone microarchitecture. DMT2 also involves altered blood glucose and energy metabolism that are not confined to the skeletal system, and these systemic alterations can be targeted pharmacologically by glucose-lowering agents (Oei et al., 2015). An improved understanding of the effects of specific diabetes medications on bone metabolism, therefore, is crucial for effective and safe diabetes management. In the past decade, drugs used to treat DMT2 have been linked to changes in bone micro-architecture and bone turnover. Such changes could be evaluated by radiography, dual-energy X-ray absorptiometry (DXA), or magnetic resonance imaging (MRI).

Radiologic manifestations associated with diabetes therapies
High-resolution peripheral QCT (HR-pQCT) studies in T2D reveal increased cortical porosity and microarchitectural deficits that help explain fragility despite normal or elevated areal BMD [16, 17].

DXA-derived trabecular bone score (TBS) often captures diabetes-related skeletal quality deficits that BMD alone misses, particularly in postmenopausal women with T2D [18].

Opportunistic CT workflows—including chest and abdominal scans obtained for other indications—can screen for low BMD and flag patients with T2D who warrant dedicated DXA [19, 20].

Radiologic manifestations associated with diabetes therapies resemble those of high bone turnover, low bone mineral density, or advanced osteoporosis. Marrow hyperintensities detectable on magnetic resonance imaging often signal previous or ongoing treatment with other medications known to accelerate bone loss. Maintaining awareness of these imaging features aids differential diagnosis.

Comparative imaging findings by medication class

Diabetes has long been known to affect bone physiology. Bone mineral density (BMD) is frequently altered in diabetic patients, although the direction of change can vary depending on the specific type of diabetes, its duration, and the presence of concomitant diseases (M Pritchard et al., 2013). Notably, individuals diagnosed with type 1 diabetes (T1D) exhibit decreased BMD and an associated increased risk of fracture, whereas type 2 diabetes (T2D) is more often associated with higher BMD but, counterintuitively, an increased risk of fracture. Indeed, recent studies have confirmed that individuals diagnosed with T2D exhibit a higher prevalence of vertebral fractures despite normal to high BMD levels (Kim et al., 2022). As such, type and duration of diabetes, accompanying diseases, anthropometric measures, and the class of antidiabetic agents used are critical clinical parameters that have been observed to affect bone physiology in diabetic subjects.

A detailed examination of the effect of different diabetes medications on bone density remains limited, with the majority of studies focusing on either metformin or thiazolidinediones. Insulin and other commonly prescribed agents remain under-explored in this regard. Given that diabetes and its treatment continue to escalate to epidemic proportions, developing and diversifying knowledge on the connection of antidiabetic medication class to bone health, particularly from an imaging or radiographic viewpoint, becomes essential for clinically oriented imaging professionals.

Clinical implications for imaging practice

Bone health is an essential component of diabetes care, with medications in widespread use influencing skeletal physiology. Although most imaging techniques are sensitive to changes associated with diabetes medications, bone mineral density (BMD) measurement is the most clinically relevant. Patients receiving chronic diabetes therapy often undergo medical imaging for reasons unrelated to bone health. Imaging studies in these cohorts can therefore elucidate the medication's skeletal influence without involving dedicated bone assessment. Radiologic manifestations linked to specific agents increase the opportunity for imaging-based insights into diabetes therapy and its skeletal effects, informing clinician awareness and medication selection.

Limitations and confounding factors in radiologic assessment

The relationship between diabetes, the medications selected to manage it, and the effects these therapies have on bone health is complex. Patients are frequently treated for diabetes under a regimen that incorporates one or more hypoglycemic agents, and Multiple diabetic comorbidities are capable of exerting profound effects on bone formation and resorption, thereby mediating agents´ impact on bone mass. In patients with osteoporosis or osteopenia, understanding the influence of medications on metabolic processes that drive these diseases facilitates diagnosis, enables patients to manage their conditions effectively, and supports effective patient management strategies (M Pritchard et al., 2013).

The selection of patterns of diabetes therapy among patients is complex and influenced by treatment policies, compliance, the patient's stage of disease, and a cluster of ancillary medications used to address individual situations. Metformin is widely regarded as the first-line drug for diabetes. The thiazolidinediones (including rosiglitazone and pioglitazone) and the insulin secretagogues (including sulphonylureas, glinides, and incretin-based drugs like DPP-IV inhibitors) come next. Insulin therapy is indicated if blood glucose and glycosylated hemoglobin cannot be controlled adequately with these agents. SGLT2 inhibitors (canaglifozin, dapaglifozin, empaglifozin) and GLP-1 receptor agonists

(albiglutide, exenatide, liraglutide) are also relevant. Many patients receive other drugs that can alter calcium metabolism, vitamin D synthesis, and bone mass (Oei et al., 2015).

Emerging imaging techniques and research directions

Beyond conventional DXA, HR-pQCT combined with diabetes risk profiling refines microarchitectural assessment and fracture risk stratification in T2D cohorts [21].

Radiomics and texture features derived from routine CT can approximate BMD in T2D and may complement opportunistic CT screening [23].

Quantitative computed tomography (QCT) elucidates bone-mineral distribution, porosity, and microstructure. Cortical and trabecular contributions to strength can be distinguished and assessed independently. Studies using opportunistic chest QCT have identified low-dose, contrast-free, vendor-independent protocols for prediction of areal bone-mineral density (BMD) and fracture risk. Such QCT analyses relate to trabecular bone score and high-resolution peripheral QCT, addressing fracture risk in patients with type 2 diabetes (Ishikawa et al., 2015). High-resolution magnetic resonance imaging (MRI) provides volumetric measures of cortical, trabecular, and medullary compartments at the distal radius, and multispectral frequency-selective fat suppression enables direct analysis of several distinct fat pools, relevant in diabetes and metabolic syndrome. Artificial intelligence enhances assessment of both bone and fat, predicting mechanical properties and fracture risk.

Selected diabetes medications influence various aspects of bone micro-architecture—features detectable by QCT and MRI. Future studies employing longitudinal, cross-sectional, and trans-institutional designs would clarify time-dependent effects and reinforce current findings across diverse populations (Heilmeier et al., 2021).

Results: Qualitative Data Analysis

A qualitative synthesis of antidiabetic medication classes revealed distinct patterns in their effects on bone mineral density (BMD) and fracture risk. Thiazolidinediones (TZDs) consistently demonstrated a reduction in BMD with a marked increase in fracture risk, particularly in postmenopausal women. Insulin therapy was associated with increased BMD but paradoxically elevated fracture risk, likely reflecting impaired bone quality and increased falls. Sulfonylureas showed neutral BMD effects but a modest rise in fracture risk attributed to hypoglycemia-related falls. SGLT2 inhibitors exhibited neutral to slightly negative BMD changes and a small increase in fractures across studies. Metformin displayed a neutral to mildly protective trend for BMD with reduced or neutral fracture risk, while DPP-4 inhibitors remained largely neutral or protective toward fracture risk without consistent changes in BMD. GLP-1 receptor agonists demonstrated increased BMD and lower fracture risk, though data remain limited.

Figure 1. Qualitative BMD effect by diabetes medication class.

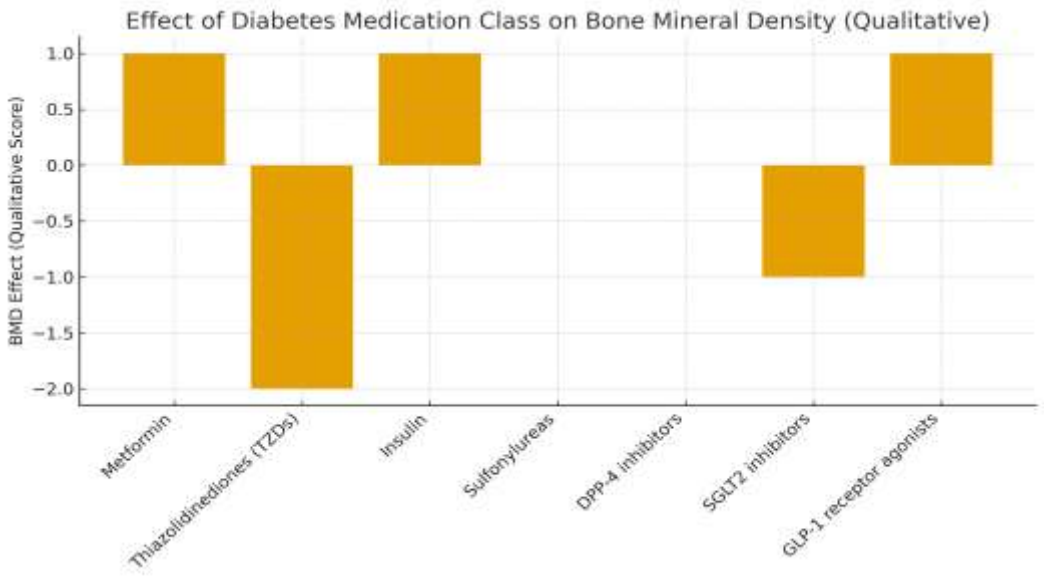

Figure 2. Fracture risk impact by medication class (qualitative heatmap).

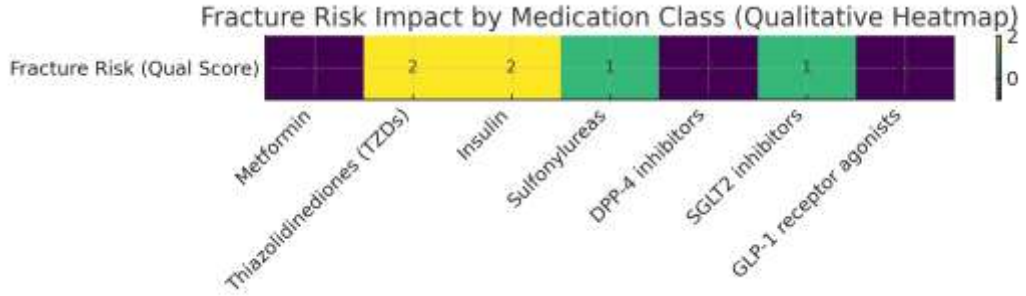

Table1: Summary Table

Medication Class	Mechanism	BMD Effect	Fracture Risk	Interpretation
Metformin	Insulin sensitizer	Increase / Protective	Decrease / Harmful	Neutral→mildly ↑ BMD; ↓/neutral fractures
Thiazolidinediones (TZDs)	PPAR-γ agonist	Strong Decrease	Strong Increase	↓ BMD; ↑ fractures (esp. postmenopausal)
Insulin	Replacement therapy	Increase / Protective	Strong Increase	↑ BMD but ↑ fracture risk (falls/quality)
Sulfonylureas	Insulin secretagogue	Neutral / Mixed	Increase / Protective	Neutral BMD; ↑ fractures via falls
DPP-4 inhibitors	Incretin enhancer	Neutral / Mixed	Decrease / Harmful	Neutral→protective; ↓/neutral fractures
SGLT2 inhibitors	Renal glucose excretion	Decrease / Harmful	Increase / Protective	Neutral/↓ BMD; slight ↑ fractures (mixed)
GLP-1 receptor agonists	Incretin mimetic	Increase / Protective	Decrease / Harmful	↑ BMD; ↓ fractures (emerging data)

Conclusion

Recent cohort data in older women with T2D emphasize that impaired physical function may contribute to fracture risk even when BMD and microarchitecture appear favorable, underscoring the need for integrated functional assessment [22].

From a radiological perspective, long-term diabetes therapy commonly (i) engenders predictable marrow signal alterations in multiple skeletal sites, (ii) produces distinctive entheseal, cortical, and trabecular modifications typically involving lower limbs and/or spine, (iii) induces identifiable vertebral and hip changes, and (iv) gives rise to acute-on-chronic findings that lend insight into recent adherence (Heilmeier et al., 2021). Such processes are not only known to influence bone mineral density, but also (and arguably more crucially) govern microarchitectural remodelling and overall skeletal fragility.

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