

Review

Diabetic Bone Disease and Fracture Healing: Molecular Mechanisms, Skeletal Fragility, and Emerging Orthopedic Therapeutic Strategies

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Abstract

Diabetes mellitus is increasingly recognized as a disorder of skeletal quality in addition to metabolic dysregulation. Both type 1 and type 2 diabetes are associated with increased fracture risk, impaired fracture healing, and higher rates of orthopedic complications despite preserved or even elevated bone mineral density, highlighting the limitations of conventional densitometric assessment alone. Diabetic bone disease arises through complex and interconnected mechanisms involving osteoblast, osteocyte, and osteoclast dysfunction, accumulation of advanced glycation end products, oxidative stress, chronic inflammation, impaired insulin and insulin-like growth factor-1 signaling, and disruption of bone–pancreas and bone–adipose crosstalk. Here, we review the cellular, molecular, genetic, and epigenetic mechanisms that contribute to diabetic skeletal fragility and examine how these abnormalities impair bone remodeling, fracture healing, and orthopedic outcomes. Particular emphasis is placed on the disconnect between bone mineral density and bone quality, describing how alterations in bone microarchitecture and matrix integrity contribute to skeletal fragility beyond the conventional measures of bone mass. We further review emerging strategies for fracture risk assessment, including advanced imaging modalities and biomarkers that more accurately characterize diabetic bone disease, and discuss the influence of antidiabetic therapies, perioperative glycemic optimization, and emerging biologic and epigenetic therapeutic approaches on fracture healing and musculoskeletal outcomes. By integrating molecular mechanisms with clinical and orthopedic evidence, this review provides a comprehensive overview of diabetic bone disease while highlighting priorities for future research and clinical translation.

Keywords: diabetic bone disease; fracture healing; skeletal fragility; bone quality; advanced glycation end products; precision medicine; regenerative medicine; orthopedic complications



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1. Introduction

1.1. Diabetes as a Systemic Skeletal Disease

Diabetes mellitus is a metabolic disorder characterized by chronic hyperglycemia resulting from defects in either insulin secretion or insulin action. The global prevalence of

diabetes is rising. In 2021, 1.66 million deaths were attributed to the disease, reflecting an age-standardized mortality growth of nearly 8% since 1990. Historically, clinical attention has been focused on microvascular and macrovascular complications, such as retinopathy, nephropathy, neuropathy, and cardiovascular disease. However, diabetes is also an important contributor to skeletal morbidity, and given the growing number of individuals living with diabetes worldwide, identifying its effects on bone health and fracture risk has become increasingly relevant to orthopedic practice [1,2].

For example, both type 1 and type 2 diabetes are associated with an increased risk of fracture, specifically at the hip and vertebrae. Type 2 diabetes, in particular, is linked to a greater risk of foot fractures. Interestingly, this increased fracture risk is not explained by bone mineral density (BMD), as type 1 diabetes patients often have lower BMD, while those with type 2 diabetes often have normal or higher BMD than patients without diabetes [3–5]. Thus, these findings suggest that diabetes contributes to skeletal fragility through factors beyond bone mass, such as alterations in bone turnover and microarchitecture that contribute to bone quality [6,7]. Therefore, conventional measures of BMD, such as dual-energy X-ray absorptiometry (DXA), may underestimate skeletal fragility in patients with diabetes [8,9].

1.2. Orthopedic Consequences of Diabetic Bone Disease

The effects of diabetes on skeletal health extend beyond an increased fracture risk and have important implications for orthopedic care. For example, patients with diabetes experience higher rates of delayed union and nonunion, particularly following fractures of the lower extremities and other non-osteoporotic fracture types. This impaired healing response is driven by diabetes-associated metabolic and inflammatory changes, such as peripheral neuropathy and vascular insufficiency, which disrupt normal bone repair, increasing the likelihood of nonunion and often requiring prolonged immobilization or revision procedures [10,11]. Elevated hemoglobin A1c levels are associated with increased rates of these bone healing complications, particularly following foot and ankle surgery [12,13].

Diabetic bone disease is also associated with higher rates of surgical site infection and implant failure, making perioperative glycemic control a key target for patient risk stratification and perioperative patient optimization [14,15]. Altogether, the effects of diabetes on fracture risk and bone healing extend beyond traditional measures of bone density. As orthopedic surgeons increasingly care for patients with diabetes, understanding the molecular and structural mechanisms that contribute to diabetic bone disease may help guide perioperative management and identify patient-specific opportunities for risk reduction.

1.3. Purpose, Scope, and Rationale

Although diabetic bone disease has received increasing clinical attention, much of the existing literature examines effects related to molecular bone alterations, fracture risk, and orthopedic outcomes in isolation. This review aims to provide a translational overview that links the molecular mechanisms of diabetic bone disease to their clinical consequences in terms of skeletal fragility and fracture healing. This study particularly emphasizes osteoblast, osteoclast, and osteocyte dysfunction; advanced glycation end products; bone–pancreas and bone–adipose crosstalk; genetic and epigenetic regulation; fracture risk assessment; biomarkers; and emerging therapeutic strategies. To maintain a focus on bone disease, diabetes-related complications such as neuropathy, vascular disease, renal disease, and soft tissue complications are only discussed when they directly influence bone integrity or repair. The review progresses from molecular mechanisms to clinical manifestations and orthopedic implications, with the goal of consolidating existing evidence to improve fracture risk prediction, fracture healing, and orthopedic outcomes in diabetic patients.

The unique contribution of this review is its emphasis on the translational relationship between diabetic bone biology and orthopedic outcomes. In addition, this review highlights emerging areas such as bone–pancreas and bone–adipose crosstalk, genetic and epigenetic regulation, biomarkers, precision medicine approaches, and therapeutic strategies not emphasized in prior reviews. By linking cellular and molecular mechanisms to fracture risk, fracture healing, and postoperative complications, this review aims to bridge the gap between basic science and clinical orthopedic practice. An overview of the principal pathogenic mechanisms linking diabetes mellitus to skeletal fragility and impaired orthopedic outcomes is presented in Figure 1.

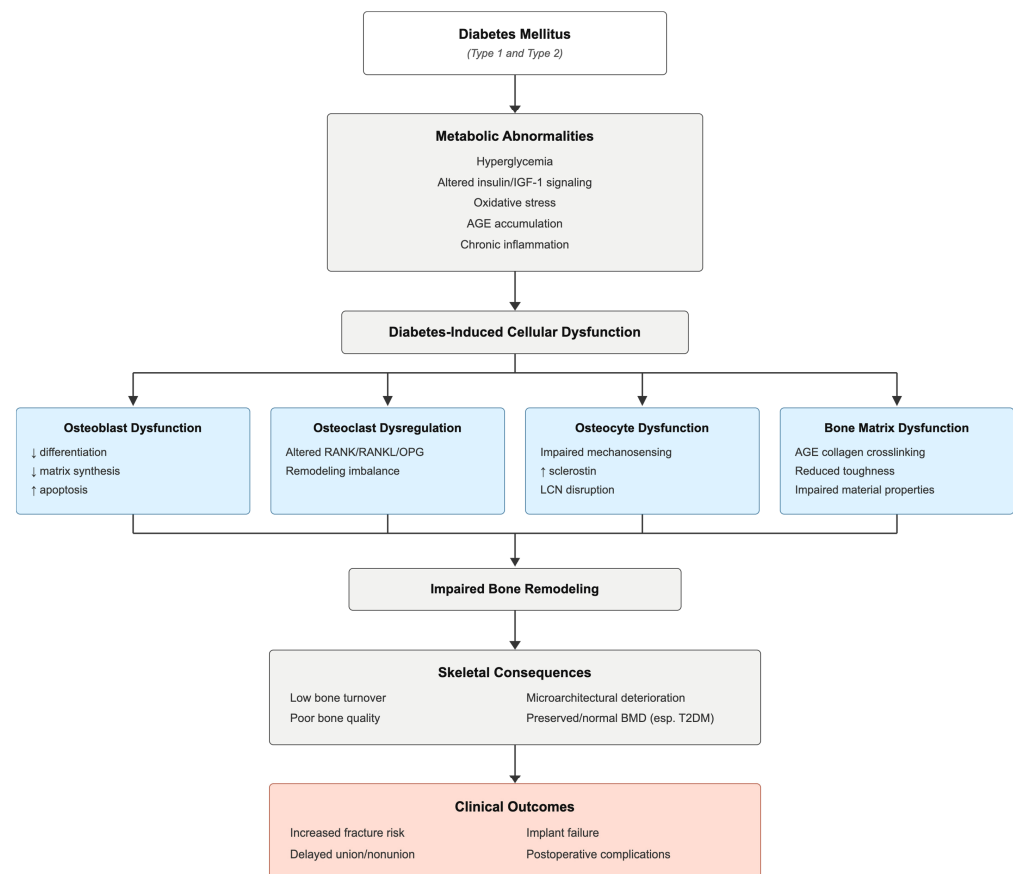


Figure 1. Pathogenesis of Diabetic Bone Disease. Schematic representation of the major biological events linking diabetes mellitus to skeletal fragility and impaired orthopedic outcomes. Diabetes-associated metabolic abnormalities initiate dysfunction across multiple bone cell populations and the extracellular matrix, culminating in impaired bone remodeling, deterioration of bone quality, and increased fracture susceptibility.

2. Cellular and Molecular Mechanisms of Diabetic Bone Disease

Diabetic bone disease results from the impact of multiple cellular defects that progressively impair bone formation, remodeling, and matrix maintenance, thereby increasing skeletal fragility. Skeletal integrity maintenance relies on the coordinated activity of osteoblasts, osteoclasts, and osteocytes. Chronic hyperglycemia disrupts this coordination through altered insulin and insulin-like growth factor-1 (IGF-1) signaling, increased generation of reactive oxygen species (ROS), and accumulation of advanced glycation end products (AGEs). Collectively, these factors produce a low-turnover skeleton that is more susceptible to fractures, even when BMD remains within normal limits.

2.1. Osteoblast Dysfunction and Impaired Bone Formation

Osteoblasts, which come from mesenchymal cells, carry out bone formation. They undergo differentiation from osteoprogenitors as a result of a transcriptional program that includes Runx2/Cbfa1, Osterix, and Wnt/ β -catenin signaling, and they regulate osteoclast activity via the RANKL/OPG axis [16]. In diabetes, bone turnover and osteoblast output are decreased by different mechanisms depending on diabetes type. In type 1 diabetes, insulin deficiency and reduced IGF-1 signaling limit osteoblast activity during skeletal growth and may restrict the achievement of peak bone mass. In type 2 diabetes, insulin resistance, hyperglycemia, and systemic inflammation inhibit osteoblast function even though insulin levels in the blood are normal or elevated [17]. Histomorphometric studies illustrate that bone from diabetic individuals has fewer osteoblasts, less osteoid, and lower levels of circulating osteocalcin [17].

2.1.1. Hyperglycemia and Impaired Osteoblast Differentiation

Hyperglycemia directly interrupts this transcriptional program. Experimental studies indicate that elevated glucose levels inhibit Runx2, reducing osteoblast lineage commitment and impairing reparative capacity [18,19]. The loss of Osterix further compromises the maturation processes needed for bone formation [20]. Additionally, AGEs worsen these effects by decreasing the expression of both Runx2 and Osterix, reducing alkaline phosphatase activity, and increasing osteoblast apoptosis [21]. Consequently, matrix mineralization fails and bone-forming capacity is permanently reduced. This persistent low-formation state throughout the remodeling cycle explains the skeletal fragility observed in diabetes, independent of BMD [22].

2.1.2. Oxidative Stress and Inflammatory Signaling

This transcriptional suppression is not an isolated event. Hyperglycemia induces oxidative stress through the formation of AGEs, activation of protein kinase C, increased polyol pathway flux, and glucose autooxidation, all leading to excessive mitochondrial superoxide production [23,24]. In bone tissue, oxidative stress suppresses osteoblast differentiation and produces a low turnover, osteopenic phenotype [25]. At the cellular level, it causes mitochondrial dysfunction which results in apoptosis and disrupts autophagy, all reducing osteoblast numbers [26]. The underlying mechanism involves ROS and AGE-RAGE signaling, which inhibit pro-survival pathways (MAPK, NF- κ B, AP-1), decrease expression of the anti-apoptotic protein Bcl-XL, and activate caspase-dependent apoptosis [27,28].

Hyperglycemia and ROS maintain a state of chronic inflammation, which in turn worsens damage to osteoblasts. When glucose levels rise acutely, the amounts of TNF- α , IL-6 and IL-18 increase, an effect which is counteracted by the administration of antioxidants, thus reinforcing the relationship between inflammation and oxidative stress [29]. TNF- α decreases the viability of osteoblasts and triggers apoptotic signaling [30]. In a clinical setting, patients with type 1 diabetes who have poor glycemic control show higher levels of IL-6 and IL-8, lower concentrations of IGF-1, and a reduced BMD, thereby demonstrating a connection between systemic inflammation and bone loss [31].

2.2. Osteoclast Dysregulation and Abnormal Bone Remodeling

2.2.1. RANK/RANKL Signaling Alterations

Bone resorption is regulated by the RANKL/RANK/OPG axis. Osteoprotegerin (OPG) inhibits the life cycle of osteoclasts by preventing RANKL from binding to RANK. The relative concentrations of RANKL and OPG determine bone mass and strength [32]. In diabetes, this regulatory balance shifts toward RANKL, and in inflammatory conditions such as diabetic foot, RANKL overexpression leads to excessive osteoclast activity and

osteolysis [33]. Tumor necrosis factor- α (TNF- α) further contributes by activating NF- κ B independently of RANK, through the TRAF6 pathway and ectopic NFATC1 activity. This process increases the RANKL/OPG ratio and promotes osteoclast formation in the bone of diabetic patients [34].

Osteoclast-related findings in diabetes are variable, reflecting differences in diabetes type, disease duration, glycemic control, and experimental models. In type 1 diabetes, increased RANKL/RANK signaling and reduced responsiveness to OPG enhance the sensitivity of peripheral blood osteoclasts. In contrast, models of type 2 diabetes demonstrate that elevated glucose concentrations suppress osteoclast formation, differentiation, and matrix-degrading function [35,36]. However, some studies report that hyperglycemia increases osteoclast resorptive capacity, mediated by resistance to inhibitory signals such as LPS-induced suppression [37,38]. These discrepancies likely contribute to the variability in bone remodeling abnormalities observed among diabetic patients.

2.2.2. Remodeling Imbalance and Skeletal Consequences

Beyond individual cell behavior, diabetes disrupts the coupling between bone resorption and formation that is essential for balanced remodeling. Resorbing osteoclasts release active TGF- β 1, which recruits mesenchymal stem cells to resorbed sites, thereby linking the resorption, reversal, and formation phases of the remodeling cycle [39,40]. When this coupling is impaired, a low-turnover state develops; formation markers such as procollagen type 1 N-terminal propeptide (P1NP), osteocalcin, and bone-specific alkaline phosphatase decrease alongside resorption marker carboxyl-terminal cross-linking telopeptides of type 1 collagen (CTX), suppressing remodeling that predicts fracture risk independently of BMD [6]. Structural consequences are confirmed by trabecular bone score and cortical porosity studies, which reveal deteriorated microarchitecture and altered bone composition in type 2 diabetes despite normal density measurements [41,42].

2.3. Osteocyte Dysfunction and Altered Skeletal Homeostasis

2.3.1. Mechanotransduction and Bone Adaptation

Osteocytes make up over 90% of bone cells and serve as the skeleton's sensory network, translating mechanical loading into remodeling signals via nitric oxide, calcium, and Piezo-mediated pathways. When their mechanosensing declines, bone turnover becomes disordered, and osteoporotic changes follow [43]. Diabetes directly damages this control system. AGE accumulation and cellular senescence impair osteocyte viability through RAGE signaling and a pro-inflammatory senescence-associated secretory phenotype (SASP) [44]. Hyperglycemia measurably blunts osteocyte sensitivity to mechanical load in both cell culture and animal models [45]. Type 2 diabetes beginning in young adulthood produces early accumulation of senescent osteocytes carrying a distinct SASP signature [46]. Diabetic bone shows disrupted lacunocanalicular network (LCN) connectivity, the channel system osteocytes use to communicate and maintain bone health, with canalicular and node densities reduced by 21% and 30%, respectively [47].

2.3.2. Sclerostin Signaling and Bone Quality

Osteocytes also govern bone formation through sclerostin, which antagonizes Wnt/ β -catenin signaling by binding Wnt coreceptors and blocking BMP-induced osteoblast differentiation [47]. Glucose concentration directly regulates sclerostin expression, supplying a specific mechanism through which hyperglycemia suppresses bone quality at the osteocyte level [48]. Consistent with this, AGE exposure raises sclerostin expression in osteocyte-like cells, though its effect on RANKL expression in osteocytes is still inconsistent across reports. Clinically, elevated circulating sclerostin predicts vertebral fracture risk in type 2 diabetes, independent of BMD and bone turnover, in both sexes [49], supporting its

relevance as a marker of diabetic skeletal fragility. Its clinical use is not yet settled, however: sclerostin may also reflect vascular changes linked to cortical porosity, and inconsistent results across assays limit interpretation [50]. Even so, sclerostin is steadily regarded as a candidate therapeutic target, with ongoing work examining if it can help predict or treat diabetes-associated osteoporosis [51].

2.4. Advanced Glycation End Products (AGEs) and Matrix Quality

2.4.1. Collagen Crosslinking and Material Properties

Diabetes affects not only the cellular components of bone remodeling but also the bone matrix itself. Collagen crosslinking, a critical post-translational modification, determines both the biological and mechanical properties of bone. AGE-derived, non-enzymatic crosslinks are believed to impair these properties compared to normal enzymatic crosslinking [52].

Normal enzymatic collagen crosslinking is initiated by lysyl oxidase (LOX) and related LOX-like enzymes, including LOXL1, which oxidize lysine and hydroxylysine residues to facilitate the formation and maturation of crosslinks that stabilize the collagen matrix [53]. This pathway is disrupted under diabetic conditions. In primary bone cells isolated from diabetic mice, LOX expression was reduced by approximately 90% and LOXL1 by approximately 50%, with impaired glucose-dependent insulinotropic polypeptide (GIP) signaling implicated in this dysregulation [54]. GIP directly stimulates osteoblasts through the adenylyl cyclase cAMP pathway, increasing LOX activity and collagen maturity [55]. Therefore, diabetic collagen deterioration likely reflects a dual defect in matrix quality with reduced physiologic LOX-dependent enzymatic crosslinking superimposed on increased pathologic AGE-mediated non-enzymatic crosslinking.

AGEs accumulate within collagen fibers, altering the organic matrix, mineral content, and water distribution in bone tissue. Circulating AGE and soluble RAGE levels correlate with fracture risk independently of BMD [56,57]. At the microstructural level, AGE accumulation is associated with reduced resistance to crack growth, compromising toughening mechanisms such as microcrack diffusion, lamellar separation, crack bridging, and deflection that normally protect bone from fracture [58]. Collectively, these findings support a model in which diabetic bone strength declines through mechanisms not detected by DXA-based BMD measurements [59].

2.4.2. Matrix Dysfunction and Skeletal Fragility

Pentosidine, a measurable non-enzymatic crosslink and surrogate marker of AGE accumulation, exemplifies the disconnect between bone strength and BMD. In diabetic animal models, increased pentosidine content correlates with reduced bone strength, including lower maximum load, energy absorption, stiffness, and elastic modulus, without corresponding changes in BMD [60]. In older adults with diabetes, elevated pentosidine independently predicts clinical and vertebral fracture incidence [61], and a meta-analysis confirms this association, with a comparatively weaker relationship to reduced BMD [62]. Not all AGE markers behave similarly: pentosidine is associated with fracture risk independent of BMD, whereas carboxymethyl-lysine demonstrates a stronger inverse relationship with lumbar BMD and correlates with sclerostin, indicating that these markers reflect different aspects of matrix injury [63]. Diabetes-driven oxidative stress, mediated by the polyol pathway, AGE formation, PKC-linked NADPH oxidase activity, and mitochondrial dysfunction, underlies both processes and shifts the balance among osteoblasts, osteocytes, and osteoclasts toward net resorption and impaired mineralization [64].

Even though this mechanism is important, interventions aimed at targeting AGEs have not been proven in a clinical setting since no clinical trial has shown that reducing the

accumulation of AGEs prevents fragility fractures, and it is only after larger studies have been carried out that the level of AGE burden can be used to guide treatment choices [65,66]. The fact that there is both cellular dysfunction and changes to the matrix caused by AGEs gives the best explanation for the increased risk of fractures in patients with diabetes even though their BMD is preserved. The major cellular and extracellular mechanisms contributing to diabetic skeletal fragility, together with their representative diabetic alterations, skeletal consequences, and orthopedic relevance, are summarized in Table 1.

Table 1. Cellular and Molecular Alterations in Diabetic Bone Disease. Summary of the principal cellular and extracellular mechanisms contributing to diabetic skeletal fragility. Representative diabetic alterations, their effects on bone biology, and their orthopedic implications are summarized for each major pathogenic pathway discussed in Section 2.

Pathway	Representative Diabetic Alterations	Skeletal Consequences	Orthopedic Relevance
Osteoblast Dysfunction	Impaired Runx2/Osterix signaling; Reduced insulin/IGF-1 signaling; Oxidative stress; Increased osteoblast apoptosis	Reduced osteoblast differentiation; Reduced matrix synthesis; Low bone formation	Delayed fracture healing; Reduced bone regeneration
Osteoclast Dysregulation	Altered RANK/OPG signaling; Remodeling imbalance; Context-dependent changes in osteoclast activity	Impaired remodeling coupling; Low-turnover skeleton	Poor remodeling; Increased fragility
Osteocyte Dysfunction	Impaired mechanotransduction; Increased sclerostin; LCN disruption	Reduced skeletal adaptation; Suppressed remodeling	Poor bone quality; Increased fracture susceptibility
AGE-Mediated Matrix Dysfunction	Increased AGE-mediated non-enzymatic crosslinking; Reduced LOX/LOXL1-dependent enzymatic crosslinking; Matrix deterioration	Reduced resistance to crack propagation; Poor mineralization	Fragility despite preserved BMD
Integrated Effect	Combined cellular dysfunction; Matrix deterioration; Suppressed remodeling	Low-turnover diabetic bone disease	Delayed union; Nonunion; Implant failure

2.5. Clinical Implications for Fracture Healing

The repair of a fracture relies on the coordinated action of all the cell types mentioned above, progressing in overlapping phases of inflammation, repair, and remodeling that depend on the presence of healthy bone-forming and bone-resorbing cells, functional osteocyte mechanosensing, sufficient vascularity, and normal matrix quality [67]. Diabetes interferes with each of these elements, via hyperglycemia, oxidative stress, chronic inflammation, impaired insulin/IGF-1 signaling, and the build-up of AGEs; and both clinical and experimental evidence consistently demonstrates delayed callus formation, impaired mineralization, slower remodeling, and higher rates of delayed union and nonunion regardless of the type of fracture or the anatomic site [10]. When viewed in this light, the abnormalities described in this section are not merely isolated observations but instead form part of a connected pathway: reduced osteoblast differentiation, dysregulated remodeling, impaired mechanotransduction, and degraded matrix quality all contribute to a failure of bone regeneration [11]. This mechanism helps to explain why an increased risk of fracture and healing problems continues even when BMD is normal and offers a basis for better risk stratification, for optimizing blood glucose levels around the time of surgery, for the development of biomarkers, and for the creation of targeted therapies aimed at restoring skeletal repair in patients with diabetes [11].

3. Metabolic Crosstalk, Genetics, and Epigenetic Regulation

3.1. Bone–Pancreas Crosstalk

Bone and the pancreas communicate through a reciprocal endocrine network that integrates skeletal remodeling with systemic energy metabolism [68]. Osteoblast-derived osteocalcin influences insulin secretion and insulin sensitivity, while insulin signaling promotes osteoblast differentiation, bone formation, and osteocalcin production in return [69,70]. Disruption of this bone–pancreas endocrine loop therefore represents an additional mechanism through which diabetes contributes to skeletal fragility beyond the direct cellular effects discussed previously [71].

3.1.1. Osteocalcin and Glucose Homeostasis

Recognizing bone as an endocrine organ has expanded the traditional view of the skeleton from a structural tissue to an active regulator of metabolism. Osteocalcin, a hormone synthesized by mature osteoblasts, is the best-studied mediator of this bone–pancreas crosstalk [72,73].

Experimental studies demonstrate that the undercarboxylated form of osteocalcin enters circulation, stimulates pancreatic β -cell insulin secretion, and enhances peripheral insulin sensitivity, acting as a bridge between skeletal remodeling and glucose homeostasis [69,74]. Human data fit this pattern: circulating osteocalcin runs lower in patients with type 2 diabetes than in healthy controls, and levels track inversely with glycemic dysregulation [74]. Combining these findings, it is suggested that disrupted osteocalcin signaling may contribute to both impaired skeletal remodeling and metabolic dysfunction [72].

Despite these observations, the endocrine role of osteocalcin remains only partially resolved. While experimental evidence strongly supports metabolic actions for undercarboxylated osteocalcin, more recent studies have proposed that osteocalcin primarily contributes to bone quality by regulating collagen organization and apatite crystal alignment as opposed to functioning as a systemic hormone [75,76]. In addition, most of the clinical evidence remains associative; more prospective human studies are needed to establish whether osteocalcin-mediated endocrine signaling is physiologically meaningful for glucose metabolism [77].

3.1.2. Reciprocal Effects of Insulin Signaling on Bone

While the endocrine role of osteocalcin continues to be investigated, the reciprocal influence of insulin on skeletal biology is well-established. Osteoblasts express functional insulin receptors, and classic experimental studies have shown that insulin receptor expression increases with osteoblast differentiation, providing evidence that bone actively responds to metabolic signals rather than simply absorbing the downstream effects of diabetes [78].

Insulin signaling promotes osteoblast proliferation, differentiation, and matrix synthesis through the Akt and ERK pathways, while IGF-1 further supports osteoblast maturation, mechanosensitive bone formation, and communication between osteoblasts and osteoclasts during bone remodeling [79,80]. Disruption of these signaling pathways contributes to skeletal abnormalities in both major forms of diabetes. In type 1 diabetes, absolute insulin deficiency and reduced circulating IGF-1 are associated with lower BMD and increased fracture susceptibility [81]. In type 2 diabetes, insulin resistance, rather than insulin deficiency, predominates and contributes to impaired bone quality despite preserved BMD. Although insulin-resistant individuals often exhibit preserved or even increased BMD, reduced osteoblast responsiveness to insulin still impairs bone formation and degrades bone quality, helping explain why fracture risk persists despite seemingly adequate bone mass [82,83].

These findings show that bone–pancreas communication runs both ways: osteocalcin shapes systemic glucose metabolism, and insulin directly governs skeletal remodeling. When this crosstalk is disrupted, it may contribute to impaired bone formation, abnormal remodeling, and skeletal fragility in both diabetes types [71].

3.1.3. Gut- and Neuroendocrine Regulation of Bone

Beyond pancreatic signaling, skeletal homeostasis is also regulated by a broader network of gut-derived and neuroendocrine signals. GIP and glucagon-like peptide-1 (GLP-1), two principal incretin hormones released from the gut in response to nutrient intake, have been implicated in the regulation of bone turnover and skeletal homeostasis [84]. GIP provides a particularly direct link between gut endocrine signaling and bone matrix quality, as it increases lysyl oxidase activity and collagen maturity in cultured osteoblasts [55], connecting incretin signaling to the LOX-dependent collagen crosslinking pathway discussed in Section 2.4.1. Skeletal remodeling is also regulated through neural and neuroendocrine pathways. Central leptin signaling influences sympathetic output, with norepinephrine signaling through β 2-adrenergic receptors on osteoblast-lineage cells contributing to the regulation of bone remodeling [85]. This central pathway is distinct from the direct peripheral effects of leptin on osteoblasts discussed in Section 3.2.2. Together, these gut- and brain-derived signals broaden the endocrine framework through which metabolic dysfunction influences skeletal homeostasis in diabetes.

3.2. Bone–Adipose Crosstalk

3.2.1. Marrow Adiposity and Skeletal Health

In addition to the endocrine interactions between bone and the pancreas, adipose tissue also plays a role in skeletal homeostasis through its local interactions within the bone marrow microenvironment. Bone marrow adipose tissue (BMAT), previously considered to be an inert fat depot, is now acknowledged as a metabolically active tissue. It contributes to skeletal physiology and metabolism by secreting bioactive factors and regulating the marrow niche [86].

Diabetes drives BMAT expansion, and higher marrow fat is consistently associated with worse skeletal health and greater fracture risk independent of BMD. Circulating lipids, visceral adiposity, growth hormone signaling, and adipokine balance likely all contribute to this shift in the diabetic marrow environment [87].

This expansion has significant biological implications, as osteoblasts and adipocytes originate from a shared mesenchymal stem cell (MSC) precursor. Under normal physiological conditions, MSCs sustain a balance between osteoblast and adipocyte differentiation. In the context of diabetes, however, hyperglycemia, oxidative stress, and inflammatory signaling redirect lineage commitment towards adipogenesis, thereby reducing osteoblastogenesis. This shift results in a decrease in osteoblast progenitors, which in turn diminishes bone formation and regenerative capacity, contributing to the low-turnover skeletal phenotype characteristic of diabetic bone disease [88].

Importantly, marrow adiposity correlates with prevalent fractures independently of BMD, suggesting that the marrow microenvironment contributes to fragility itself, not just a byproduct of low bone mass. BMAT expansion is one clear link between metabolic dysfunction and compromised skeletal repair in diabetes [87].

3.2.2. Adipokines and Skeletal Regulation

Beyond its local effects within the marrow cavity, adipose tissue also regulates skeletal homeostasis through endocrine signaling [89]. Adipose tissue secretes numerous bioactive factors, collectively termed adipokines, that regulate metabolism, inflammation, and bone remodeling, which in turn influence skeletal cell function [90].

Leptin is the most studied of these adipokines. Experimental studies demonstrate that leptin promotes osteoblast proliferation and differentiation, increases synthesis of bone matrix proteins including type I collagen and osteocalcin, and suppresses osteoclastogenesis by reducing RANK expression in osteoclast precursors, generally promoting bone formation and limiting bone resorption [91]. Adiponectin provides a complementary anabolic signal by promoting osteogenic differentiation of MSCs and enhancing osteoblast proliferation via AdipoR1-mediated activation of p38 MAPK and JNK signaling pathways. In conjunction, leptin and adiponectin demonstrate how adipose-derived endocrine signals participate in normal skeletal remodeling [92].

Diabetes disrupts this adipokine balance. Patients with type 2 diabetes often show reduced adiponectin alongside altered leptin signaling, changes that align with the low-turnover phenotype. While it is not yet clear how much each adipokine contributes, the dysregulation likely collectively worsens bone remodeling and adds to diabetic skeletal fragility [17].

These endocrine interactions demonstrate that bone functions within a broader metabolic organ network in which pancreatic and adipose tissues cooperatively regulate skeletal homeostasis. This perspective provides a framework for understanding how inherited genetic variation may further modify susceptibility to diabetic skeletal disease.

3.3. Genetic Contributors to Diabetic Bone Disease

3.3.1. Bone Remodeling Pathways

Although metabolic disturbances drive much of diabetic bone disease, inherited genetic variation may influence how individual patients respond to these skeletal stresses. Many of the signaling pathways that regulate osteoblast and osteoclast activity are under genetic control, suggesting that individual differences in these pathways may influence susceptibility to diabetic skeletal disease.

Canonical Wnt/ β -catenin signaling regulates osteoblast differentiation and bone formation by promoting osteoprogenitor expansion, osteoblastogenesis, and osteoblast survival, while the genetically regulated RANK/RANKL/osteoprotegerin (OPG) axis governs osteoclast differentiation and bone resorption [32,33,93]. As discussed previously, diabetes disrupts both pathways through chronic hyperglycemia, AGE accumulation, oxidative stress, and inflammatory signaling, with growing evidence suggesting that Wnt signaling and AGEs are major contributors to skeletal fragility in type 2 diabetes [94].

Genetic variation within these remodeling pathways has also been associated with differences in BMD and fracture susceptibility [95]. For instance, polymorphisms within RANK and OPG have been linked to variation in volumetric BMD, supporting the idea that inherited differences in remodeling capacity contribute to skeletal phenotype [96].

Rather than acting independently, genetic variation and diabetic metabolic stress likely interact to determine the extent of skeletal deterioration, providing one explanation for why patients with otherwise similar diabetic profiles may experience markedly different skeletal outcomes.

3.3.2. Susceptibility to Fracture and Skeletal Complications

Although disruption of bone remodeling pathways is a hallmark of diabetic bone disease, skeletal outcomes vary substantially among affected individuals. Patients with similar glycemic control, disease duration, and BMD may experience markedly different risks of fracture and impaired skeletal repair, suggesting that inherited susceptibility contributes to this clinical heterogeneity [97]. Moreover, fracture risk differs between diabetes subtypes, increasing approximately six-fold in type 1 diabetes because of reduced bone mass and nearly two-fold in type 2 diabetes despite preserved or elevated BMD [98].

The heritable basis of skeletal fragility has been well-established in the general population. Family and twin studies estimate that up to 80% of the variation in BMD is genetically determined, while genome-wide association studies (GWASs) have identified hundreds of loci associated with BMD, skeletal architecture, and fracture susceptibility, including genes involved in Wnt signaling and osteoblast differentiation [99,100].

Whether these genetic determinants similarly modify diabetic skeletal disease remains an area of active investigation. Candidate gene studies have implicated variants within pathways that influence both glucose metabolism and bone biology, including polymorphisms of TCF7L2, proposing that metabolic regulation and skeletal remodeling may share overlapping genetic architecture [101]. Likewise, Mendelian randomization analyses indicate that genetically predicted type 2 diabetes may be associated with higher BMD, yet this relationship does not consistently translate into lower fracture risk after accounting for obesity, vascular disease, neuropathy, and other diabetes-related complications [102].

Although current evidence does not support routine genetic screening for diabetic skeletal disease, continued advances in human genomics may improve individualized fracture-risk assessment by identifying patients with increased genetic susceptibility to skeletal complications. Importantly, inherited genetic variation represents only one component of disease risk; accumulating evidence suggests that environmentally driven modifications of gene expression also contribute substantially to diabetic skeletal fragility, providing the basis for the epigenetic mechanisms discussed in the following section [103].

3.4. Epigenetic Regulation and Emerging Therapeutic Targets

3.4.1. MicroRNAs and Skeletal Remodeling

While inherited genetic variation influences susceptibility to diabetic bone disease, epigenetic mechanisms dynamically regulate gene expression in response to the metabolic environment. Among these, microRNAs (miRNAs) are short non-coding RNAs that regulate gene expression at the post-transcriptional level and have emerged as important modulators of osteoblast differentiation, osteoclastogenesis, adipogenesis, and bone-cell function [104].

Rather than regulating individual genes in isolation, miRNAs coordinate multiple signaling pathways that govern osteogenesis. Numerous miRNAs influence TGF- β /BMP and canonical Wnt/ β -catenin signaling by modulating transcription factors such as RUNX2 and Osterix, thereby regulating osteoblast differentiation and bone formation [105]. Because individual miRNAs simultaneously influence numerous molecular networks, they represent an important layer of gene regulation during normal bone maintenance and repair [106].

Diabetes substantially alters this regulatory landscape. Chronic hyperglycemia and oxidative stress induce widespread changes in miRNA expression that disrupt cellular programs controlling proliferation, differentiation, apoptosis, and inflammatory signaling. Within skeletal tissue, these alterations may suppress osteogenesis and contribute to progressive deterioration of bone quality under persistent metabolic stress [107].

Inherited variation may further modify these effects. Single-nucleotide polymorphisms (SNPs) within miRNA genes or their target-binding sites can alter miRNA-mRNA interactions, providing an additional mechanism through which genetic susceptibility and diabetic metabolic stress converge to influence bone phenotype [108]. These findings identify miRNAs as a dynamic regulatory interface through which the diabetic metabolic environment reshapes gene expression and bone-cell behavior.

3.4.2. DNA Methylation and Histone Modification

Whereas microRNAs provide rapid post-transcriptional regulation, DNA methylation and histone modifications produce more durable changes in gene expression by altering chromatin accessibility without changing the underlying DNA sequence. These epigenetic mechanisms regulate genes controlling osteoblast differentiation, osteoclast activity, and MSC fate, thus influencing long-term bone formation and maintenance [109].

Experimental studies demonstrate that histone acetylation promotes transcription of osteogenic genes, whereas histone deacetylation and DNA methylation suppress expression of key regulators including RUNX2, OSX, ALPL, and osteocalcin. Conversely, inhibition of histone deacetylases enhances osteoblast differentiation while limiting osteoclastogenesis, highlighting the importance of chromatin regulation in maintaining balanced bone turnover [109].

Unlike transient signaling events, these epigenetic modifications may persist after the original metabolic issue has resolved. Chronic hyperglycemia can induce persistent alterations in DNA methylation and histone-marking patterns that remain after restoration of normoglycemia, a phenomenon known as metabolic memory. Although initially described in diabetic vascular disease, this concept provides a plausible explanation for why abnormalities in bone quality may persist despite subsequent improvements in glycemic control [110].

Epigenetic regulation also influences lineage commitment within the marrow cavity. Dynamic methylation changes accompany osteogenic differentiation, whereas diabetic metabolic stress may shift MSC differentiation toward adipogenesis at the expense of osteoblastogenesis, reinforcing the marrow adiposity phenotype discussed previously [111,112].

3.4.3. Therapeutic Potential of Epigenetic Targeting

The reversibility of epigenetic regulation has generated considerable interest in developing therapies that restore normal patterns of gene expression in diabetic bone disease. Studies of diabetic complications have demonstrated that modulation of histone acetylation, DNA methylation, and microRNA signaling can attenuate epigenetic alterations associated with metabolic memory, raising the possibility that similar strategies could improve skeletal repair and preserve bone quality [113].

Among these approaches, therapeutic modulation of dysregulated miRNA expression has shown promise for restoring osteogenic signaling and promoting bone regeneration in preclinical models. However, limited in vivo stability, challenges in tissue-specific delivery, and potential off-target effects remain important barriers to clinical translation [114].

Pharmacologic modulation of chromatin remodeling through histone deacetylase and DNA methyltransferase inhibitors has likewise demonstrated encouraging effects on osteogenic differentiation and bone regeneration in experimental models, although evidence supporting clinical application remains limited [115,116].

Emerging molecular tools, including epigenetic clocks, may eventually help identify patients most likely to benefit from targeted epigenetic therapies. Despite these approaches remaining investigational, they illustrate how molecular characterization of diabetic bone disease could support increasingly individualized therapeutic strategies [117].

3.5. Clinical Implications for Risk Stratification

The endocrine, genetic, and epigenetic mechanisms discussed throughout this section demonstrate that diabetic skeletal disease cannot be fully explained by alterations in BMD alone. Accordingly, conventional fracture-risk assessment tools such as DXA and the Fracture Risk Assessment Tool (FRAX) frequently underestimate skeletal risk in diabetes,

particularly in patients with type 2 diabetes who often present with preserved or increased BMD despite impaired bone quality [3,7].

The pathways described in this section illustrate that endocrine signaling, inherited genetic variation, and environmentally responsive epigenetic regulation each capture distinct aspects of skeletal biology that are not reflected by conventional imaging alone. Molecular biomarkers derived from these pathways, including osteocalcin, adipokines, marrow adiposity, genetic variants, and epigenetic signatures, may therefore complement existing clinical assessment by providing insight into inherited susceptibility and cumulative exposure to hyperglycemia and chronic inflammation [17,74,87,102,117].

Although these approaches are being actively investigated, future assessment of diabetic skeletal disease will likely integrate conventional clinical evaluation with advanced imaging, circulating biomarkers, genetic susceptibility, and epigenetic profiling to provide a more comprehensive understanding of skeletal health than any single measure alone. Together, the endocrine, genetic, and epigenetic mechanisms discussed in this section establish the biologic framework through which the clinical manifestations of diabetic bone disease can be understood (Figure 2) [7].

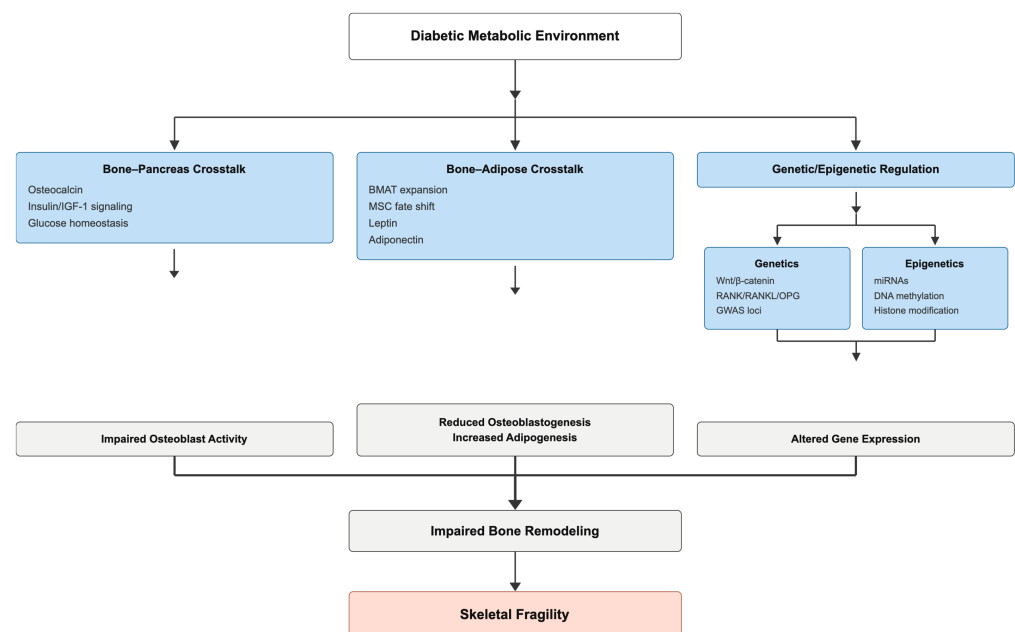


Figure 2. Metabolic Regulation of Diabetic Bone Disease. Schematic representation of the major endocrine, genetic, and epigenetic pathways regulating skeletal homeostasis in diabetes. Each regulatory axis converges on impaired bone remodeling through distinct but interconnected mechanisms, ultimately culminating in skeletal fragility.

4. Factors Influencing Orthopedic Risk and Surgical Outcomes

4.1. Skeletal Fragility and the Bone Density Paradox

As stated, studies and tests frequently indicate that patients with diabetes experience impaired bone quality and increased fracture risks. Traditional methods of monitoring fracture risk often rely on BMD, but this marker may not be reliable for determining the fracture risk for patients with diabetes. This is especially true for those with type 2 diabetes mellitus (T2DM), as T2DM patients often have normal or elevated BMD with an elevated fracture risk simultaneously [3]. This discrepancy is termed the Bone Density Paradox, and it is a result of underlying abnormalities involving bone quality rather than bone quantity or density. These abnormalities include the biological mechanisms discussed in Sections 2 and 3, including osteoblast dysfunction, osteocyte alterations, impaired re-

modeling, and AGE accumulation, all manifesting clinically as reductions in bone quality that are not fully captured by conventional BMD assessments. This has become more apparent as advanced imaging techniques have revealed microarchitectural deterioration in T2DM patients' bone structures, making bone quality assessments increasingly salient to determining fracture risk, orthopedic implications, and surgical recovery outcomes [3].

4.1.1. Bone Quality Versus Bone Density

It has become more apparent with advanced imaging that BMD does not adequately reflect skeletal strength in patients with diabetes, as alterations in bone quality can contribute substantially to fracture risk, including alterations that do not show up on conventional methods of measuring bone density. Looking at the bone quality in patients with diabetes has made this more apparent with the bone density and fracture paradox. The literature published in 2007 and onwards has indicated that hip fracture risk is elevated in both type 1 diabetes mellitus (T1DM) and T2DM. Paradoxically, DXA scans also reveal that BMD in T2DM is often normal or higher than BMD in individuals without diabetes mellitus (DM). T1DM patients do have lower BMD than individuals without DM, which further increases fracture risk in T1DM. However, T2DM-increased fracture risk importantly indicates that there is a mismatch between BMD and observed fracture risk due to various factors, including microarchitectural alterations [3]. Non-structural differences between patients with DM and those without are important to note. Certain fracture types are more prevalent in DM due to a greater number of falls in those with diabetic retinopathy, exacerbating the fracture risk already present due to decreased bone quality and toughness [118]. It is also important to note that on average, patients with T2DM have elevated body mass index (BMI), greater mechanical loading, and increased DXA-derived BMD than individuals without T2DM, leading to greater densitometric measures despite persistent lower bone quality and skeletal fragility [3].

This phenotype, however, is not uniform across T2DM. Higher body mass increases mechanical loading and may stimulate the adaptive skeletal responses described in Section 2.3.1, contributing to the higher BMD frequently observed in patients who are overweight or obese [119]. In a nationwide cohort of more than 2.7 million patients with T2DM, fracture risk was highest in underweight patients and progressively lower in the obese and morbidly obese groups relative to patients of normal weight, indicating that normal-weight patients with T2DM do not share the same BMI-associated reduction in fracture risk observed in their higher-BMI counterparts [120]. This distinction is increasingly relevant, as lean/normal-weight T2DM is now recognized as a distinct and understudied phenotype rather than a rare exception [121]. Elevated body mass also does not necessarily translate into proportional osteogenic benefit. Although greater body weight increases mechanical loading, skeletal adaptation is also influenced by weight-bearing physical activity and muscle-generated mechanical strain; reduced muscle function and prolonged sedentary behavior may therefore attenuate the skeletal benefits otherwise associated with greater body mass [119,122]. Body composition and habitual mechanical loading, rather than BMI alone, should therefore be considered when interpreting the apparent preservation or elevation of BMD in T2DM.

Bone quality, rather than density, includes matrix properties, microarchitecture, turnover, and mineralization qualities of the bone. Both quality and density are important in determining bone strength, and diabetes tends to affect quality rather than density [59]. The presence of these qualitative features repositions the discussion of bone strength and fracture risk to be one within a clinical framework, integrating numerous properties rather than a quantitative discussion about DXA-derived BMD alone. This has clinical implications, as matrix properties and microarchitecture can be observed via advanced markers

and imaging techniques (Serum sclerostin levels, trabecular bone score, high resolution peripheral quantitative CT, bone marrow fat saturation, and AGEs) that can measure bone cell function and fracture risk in diabetes [6]. For clinical impact, these advanced techniques become increasingly salient in fracture-risk management in diabetes and moving away from relying on BMD alone. As an example, AGE-mediated collagen alterations were introduced in Section 2.4 and how they impact the mechanical performance of bone and fracture susceptibility [56]. Plasma and urinary levels of AGEs have been proposed as candidates for estimating bone quality in diabetes, and inhibiting the formation of AGEs has been proposed as a method for reducing fracture risk [123]. This is one example of how assessing cell function and microarchitectural properties of bone can have clinical impact that moves decision-making away from being dictated by BMD alone.

Current tools (FRAX and DXA) have limitations and are simply unable to adequately explain all of the microarchitectural factors that contribute to bone fragility in diabetes. Two-dimensional DXA-scans of BMD have long been routine for predicting fracture risk in diabetes because osteoporosis is a skeletal side effect of diabetes. Two-dimensional images have limitations and can underestimate fracture risk simply due to inadequate evaluation of bone strength. The microarchitectural damages discussed throughout this review cannot be summed up by two-dimensional scans, making volumetric BMD and microarchitecture studies superior to DXA in predicting future fractures [124]. FRAX is a more recent fracture risk assessment method that combines age, sex, BMI, glucocorticoid use, smoking, alcohol intake, secondary osteoporosis, rheumatoid arthritis, prior fragility fractures, and femoral neck BMD T-score to generate estimated 10-year hip fracture risks. FRAX has been shown to be better at predicting this than BMD T-score alone. However, FRAX was also shown to underestimate osteoporotic and hip fracture risk in diabetes patients, concluding that diabetes fracture risk has contributing factors independent from those in FRAX derived with BMD [125]. Therefore, current tools underestimate diabetic skeletal fragility, making a clinical diagnosis based on advanced methods that take into account microarchitectural, biomarker, and cell function variations more reliable.

4.1.2. Microarchitectural Alterations

Bone quality abnormalities are difficult to detect using DXA alone, but advanced imaging techniques permit assessment of bone microarchitecture that is shown to influence fragility. High-resolution peripheral computed tomography (HR-pQCT) is an example of advanced imaging that is a low-radiation dose procedure (3–5 uSv) used to image bone microarchitecture and has been noted to potentially assist our understanding of the underlying mechanisms of pathophysiology in diseases like DM [126]. This was noted because HR-pQCT was shown to differentiate fracture risk between patients with only moderately low BMD but severe microarchitectural loss. This distinction would make HR-pQCT have important clinical implications for the decision to perform interventions among patients with normal or slightly low BMD. This is very relevant for patients with T2DM who may have normal BMD but microarchitectural losses. T2DM has been shown to be characterized by increased cortical porosity and decreased cross-sectional area of bone while maintaining trabecular bone. This leads to some deficits undetectable by DXA but detectable by HR-pQCT [127]. While imaging cortical and trabecular bone microarchitecture via HR-pQCT is possible, the improvement it gave to multivariate models was relatively small in studies [126]. While helpful with potential implications for T2DM, it has not been deemed the superior model.

Despite T2DM maintaining trabecular bone and giving a higher areal BMD than in individuals without T2DM, T2DM has been shown to have a lower trabecular bone score (TBS) than non-diabetic individuals. This makes TBS a useful measure when assessing

fracture risk in T2DM [128]. TBS was developed as a clinical tool to assess bone microarchitecture once DXA was found to be insufficient in assessing microarchitectural factors on bone strength. TBS analyzes gray-scale and pixel variations in 2D-projected DXA-scans to give an indirect score of the bone microarchitecture [129]. TBS has been shown to predict osteoporotic lumbar fractures in those with diabetes and account for more of the diabetes-associated fracture risk than BMD [130]. However, there is not sufficient evidence to indicate TBS as a reliable indicator of bone microarchitecture alone [129].

Although TBS provides information distinct from areal BMD, it is not acquired as an independent imaging study. TBS is instead calculated retrospectively from the two-dimensional lumbar-spine DXA image rather than acquired through a separate imaging procedure [131,132]. Although hip-derived TBS has been explored using a beta algorithm, evidence remains preliminary, and current ISCD clinical recommendations remain focused on lumbar-spine TBS [132,133]. The TBS software algorithm has also recently undergone a substantial revision (TBS iNsight version 4.0), replacing BMI-based adjustment for soft tissue effects with direct measurement of tissue thickness from DXA [134]. Although fracture-prediction performance and TBS-adjusted FRAX estimates were similar between versions at the population level, individual differences between algorithms were influenced by BMI, tissue thickness, and regional adiposity [134]. Studies using earlier TBS algorithm versions should therefore be interpreted with some caution when compared with those using the current software.

Lower TBS has also been associated with poorer glycemic control, including higher HbA1c, in patients with T2DM; however, current evidence does not establish a specific HbA1c threshold at which the diagnostic performance of TBS is optimized [135].

Cortical bone and cortical porosity have recently been found to be a step above TBS in assessing bone microarchitecture, making imaging of cortical porosity increasingly important. Cortical bone has five major types of porosity: marrow cavity, artery channels, vascular porosity, lacuno-canalicular porosity, and nano-porosity (collagen and hydroxyapatite crystals). Vascular porosity may be 'primary' canals or 'secondary' canals, which are the products of tissue turnover and remodeling. Cortical porosity is vital, as the cortex bears a lot of axial and bending loads that are applied to bones. In relation to porosity, cortical bone's elastic modulus has been shown to be related to porosity to the 10.9th power, meaning small changes in porosity equate to large changes in cortical bone's modulus. As a result, cortical porosity has been proposed as a quantifiable marker of bone fragility, and in vivo imaging processes are being pursued. Animal models are being developed to assess in vivo imaging of cortical porosity, and recent advances in phase contrast techniques make advancing in vivo imaging to preclinical models a promising prospect [136]. This is very important when considering potential imaging and microarchitecture assessment for patients with DM, as cortical porosity was found to be elevated in older patients with DM. Higher cortical porosity and cortical pore volume was observed in the distal tibia of men with DM compared to those without DM. Higher cortical pore volume was found in the distal radius in women with DM compared to those without DM. Taken together, the data here further strengthens the idea that intracortical bone loss and cortical porosity are significant complications of diabetic bone disease [41]. This could mean compromised bone mechanical/weight-bearing properties for those with diabetes and an increased fracture risk.

Clinically, it will be important to monitor microarchitectural abnormalities, especially cortical abnormalities, when assessing fracture susceptibility. While T1DM does have a relative decrease in BMD, that has not been found to fully account for the 7-fold increase in hip fracture risk compared to the general population and 5-fold risk increase compared to those with T2DM [137]. In comparison, T2DM does have normal, or even elevated, BMD,

yet still exhibits greater fragility. In one study, HR-pQCT of a T2DM cohort found 10% higher trabecular volumetric BMD adjacent to the cortex and higher trabecular thickness in the tibia than the non-T2DM cohort. Cortical porosity differences alone were consistent with impaired bone strength in the radius, and pore volume differences were significant in the tibia as well [138]. These findings indicate both that BMD is insufficient in assessing fracture risk alone and that inefficient redistribution of bone mass may account for elevated fracture incidence in T2DM despite normal/high bone mass. Intracortical bone loss in this redistribution and greater cortical porosity supports previous discussion of cortical porosity being a promising factor to monitor clinically in the future when assessing T2DM fracture risk [138]. Collectively, it has been well-demonstrated that diabetic skeletal fragility reflects abnormalities that extend beyond conventional density measurements, motivating the development of advanced techniques and biomarkers for more accurate fracture risk assessment and clinical management. The major imaging modalities, biomarkers, and clinical assessment tools currently used to evaluate diabetic skeletal fragility are summarized in Table 2.

Table 2. Clinical Assessment Tools and Emerging Biomarkers for Skeletal Fragility in Diabetes. Summary of conventional imaging tools, bone turnover markers, advanced imaging modalities, and emerging biomarkers used to evaluate skeletal fragility in diabetes. Clinical utility, principal strengths, and important limitations are summarized based on the evidence discussed in Section 4.

Biomarker/Tool	Measures	Clinical Strength	Major Limitation
DXA	Bone mineral density	Widely available	Underestimates diabetic fracture risk
FRAX	Clinical fracture risk	Improves prediction over BMD	Still underestimates diabetic fracture risk
TBS	Trabecular microarchitecture	Improves fracture-risk prediction	Indirect measure
HR-pQCT	Microarchitecture	Detects cortical porosity and microarchitecture	Limited clinical availability
Bone Turnover Markers	Representative biomarkers: P1NP, CTX, Osteocalcin, BSAP	Assess remodeling	Reduced usefulness in low-turnover diabetes
Sclerostin	Osteocyte dysfunction	Associated with fracture risk	Clinical role not yet established
Pentosidine	AGE accumulation	Reflects matrix quality	Investigational
CML	Matrix deterioration	Associated with collagen damage	Requires additional validation
Integrated Assessment	Advanced imaging, biomarkers, clinical risk factors	Most comprehensive risk assessment	Not yet standardized

4.2. Biomarkers of Bone Quality and Fracture Risk Assessment

As discussed in Section 4.1.1, conventional imaging methods, such as DXA and FRAX, can underestimate fracture risk in diabetes. In addition to advanced imaging, novel biomarkers and risk prediction tools are of interest when trying to adequately capture skeletal fragility in DM patients. Traditional bone turnover biomarkers have been used to gain information about bone remodeling activity, but these may have limitations in diabetic populations. Biomarkers in this discussion refer to circulating biochemical markers and measurable indicators of skeletal health that give surrogate measures of bone quality, like trabecular bone scores, for example. Other emerging biomarkers may provide more

insight into bone quality, osteocyte dysfunction, AGE accumulation, and microarchitectural deterioration. Integrating these emerging biomarkers with advanced imaging and clinical risk factors may have clinical significance in improving fracture-risk prediction.

4.2.1. Traditional Biomarkers

Traditional biomarkers have been used to gain insight into skeletal remodeling processes. High levels of bone remodeling have been associated with more severe osteoporosis and increased fracture risks [139]. Traditional biomarkers include formation markers that reflect osteoblast activity and resorption markers that reflect osteoclast activity, and these respond quicker to turnover than other methods like imaging. For resorption, common markers that are measurable and produced by collagen breakdown include amino-terminal cross-linking telopeptides of type 1 collagen (NTX), CTX, tartrate-resistant acid phosphatase (TRACP-5b), pyridinoline cross-links (PYD), and deoxypyridinoline cross-links (DPD). For formation, markers that are measurable and produced by highly active osteoblasts include serum osteocalcin, serum alkaline phosphatase, bone-specific alkaline phosphatase, serum P1NP, and procollagen type 1 C-terminal propeptide (P1CP). All these markers are expected to be elevated in bone undergoing high rates of remodeling (lots of formation and resorption). For this reason, these biomarkers have often been used in clinical trials and population studies assessing the efficacy of osteoporosis treatments and the ability to predict fracture risk independent of BMD [139,140]. However, these traditional biomarkers may be insufficient in assessing fracture risk in low-bone-turnover states. Diabetes, being categorized as a low-turnover skeletal state, means that traditional remodeling biomarkers may not be elevated or significant, even in instances of low bone quality. Regardless of BMD, the biomarkers osteocalcin, P1NP, alkaline phosphatase, and CTX have been shown to be decreased in T2DM, marking it as a low-turnover state. PTH also tends to be 20–50% lower in T2DM than controls, even in patients with reduced eGFR, suggesting lower PTH secretion bone resorption/remodeling [6]. In addition to not being applicable to T2DM/low-turnover states, traditional bone turnover markers (BTMs) have other notable limitations. BTMs are not highly specific, as they simply reflect the overall skeletal turnover rate rather than any specific site. BTMs also lack reliable, standardized reference values, as they often vary from patient to patient in daily clinical practice due to varying comorbidities and preanalytical factors [141]. In addition to not having truly standard measurements, it is still too early to tell whether BTMs can effectively predict impaired fracture healing processes at an early stage [142]. These limitations taken together are why the clinical utility of BTMs remains limited [141]. In the more specific discussion of T2DM, they simply do not capture the microarchitectural abnormalities that characterize diabetic bone disease.

4.2.2. Emerging Biomarkers

The inability to apply traditional bone remodeling biomarkers to assess bone quality in T2DM has motivated the pursuit of other emerging biomarkers that more completely explain diabetic fracture risk. The increasing recognition of diabetic skeletal fragility as a disorder of bone quality has also motivated the pursuit of other biomarkers. Emerging biomarkers of interest seek to measure osteocyte dysfunction, matrix deterioration, and microarchitectural damage. These newer biomarkers aim to characterize the bone quality itself, rather than simply the rate of bone remodeling. This makes them clinically significant for our discussion about T2DM and other low-turnover states where fracture risk is driven by impaired bone quality rather than abnormal turnover alone. Combining emerging biomarker panels may prove to be better for diabetic fracture risk prediction than DXA and/or FRAX alone.

Sclerostin has emerged as a biomarker to assess osteocyte dysfunction in diabetic bone disease. In states of osteocyte dysfunction, sclerostin is markedly elevated, reducing the WNT signaling pathway and reducing overall bone formation (discussed in Section 2.3.2) [51]. This pathway has motivated the exploration of sclerostin as a potential fracture-risk marker. Sclerostin has been found to be higher in both T1DM and T2DM patients, and there is a possible association between sclerostin and low bone turnover in diabetes [50]. Sclerostin being elevated for years in DM patients can contribute to reduced bone turnover, accumulation of microdamage (microcracks and fragility fractures), accumulation of AGEs and stiffening of collagen, failure of targeted remodeling, cortical porosity, and trabecular deterioration [50]. For clinical significance, observing chronic elevations of sclerostin may lead clinicians to begin thinking about suppressed bone remodeling, accumulation of microdamage, lower bone quality, and increased fracture susceptibility in diabetic populations despite preserved BMD. As discussed in Section 2, diabetic osteocyte dysfunction is characterized by increased expression of remodeling inhibitors like sclerostin, and at the tissue level this can lead to a low-turnover phenotype with progressive deterioration of bone quality, much like T2DM. This relationship has been demonstrated in one study where elevated sclerostin levels were associated with increased vertebral fracture risk independent of BMD in T2DM [49]. Due to this relationship and pathway being found, serum sclerostin has emerged as a potential biomarker and target to help predict and treat/prevent osteoporosis and fractures in DM patients [51].

Matrix quality biomarkers that can assess matrix deterioration have emerged as possibly clinically significant. Matrix quality biomarkers include pentosidine and CML (AGEs), and the mechanisms of these were discussed in Section 2.4. Their mechanisms have allowed pentosidine and CML to function clinically as measurable surrogates of matrix deterioration's contribution to fracture risk. These markers also hold clinical significance in our more specific conversation about T2DM, as CML has been shown to mainly be associated with collagen network degradation [63]. This led to impaired bone quality and higher fracture risk independent of BMD levels. Furthermore, increased CML was associated with increased sclerostin [63]. Both of these findings make CML clinically relevant for T2DM, a low-turnover, normal-to-high BMD bone state. This was further supported by a study that found higher pentosidine levels to be a contributor to fracture risk in older patients with DM, making it a potentially clinically relevant part of assessing bone quality in T2DM, regardless of BMD [61].

Already discussed in Section 4.1.2, TBS emerged as a surrogate marker of structural quality, so it is important to mention again here. While it is derived from DXA-imaging and is not a circulating biomarker measurement, it still stands as a marker that has advantages over DXA alone that have already been discussed. Two advantages of TBS include it being a better reflection of trabecular/microarchitectural integrity than DXA or BMD alone, and it being shown to improve fracture risk prediction in patients with DM [128,130].

When discussing the future of biomarkers in helping make clinical predictions of fracture risk, it is important to recognize that no single biomarker can fully capture the spectrum of diabetic skeletal fragility and the various factors that influence it. Future clinical assessment will likely require the integration of biomarkers, advanced imaging, traditional tools (DXA and FRAX), and clinical risk factors. Taken together, these can lead to more accurate predictions for individual patients, and this is a motivation for further investigation into skeletal parameters and biomarkers that could assist our understanding of T2DM bone fragility despite normal-to-high BMD [6].

4.3. Impaired Fracture Healing, Delayed Union, and Nonunion

Another clinically relevant aspect of diabetic bone disease is its impairment of the normal healing cascade that leads to impaired fracture healing, delayed union, and nonunion. Section 2.5 discussed how DM can impair different aspects of normal fracture healing, and clinically these manifest with impaired healing outcomes and serious consequences.

4.3.1. Inflammatory Phase Dysregulation

Normal repair of fractured bone can be separated into a sequence of events: inflammatory, repair, and remodeling phases. Normal fracture healing begins with a tightly regulated inflammatory response in response to blood vessel rupture inside the fracture bone site and surrounding soft tissues. The usual characteristics of acute inflammation are present, as vasodilation and plasma and leukocytes begin to exude. In the fracture space, fibrin is formed and a fracture hematoma results. This hematoma holds peripheral blood-derived inflammatory cells, acts as a scaffold for the site, and helps recruit cytokines and inflammatory cells. This inflammatory response usually triggers the repair cascade [143].

Systemic inflammation, with DM as an example, has been found to increase fracture healing time due to its effects on the inflammatory process at the fracture site and other mechanisms not fully understood yet [143]. This is why increased fracture healing times and greater complications like non-unions are clinically significant when assessing patients with various systemic inflammation states (rheumatoid arthritis, DM, trauma, sepsis) [143].

One of the cytokines recruited to a fracture site in the inflammatory phase is tumor necrosis factor- α (TNF- α), and this cytokine helps govern MSCs and the following healing processes [144]. A study found that there may be an optimal level of TNF- α during early stages of wound healing. They demonstrated this by showing that DM led to a systemic inflammatory state, significantly increased TNF- α levels, and a resultant decrease in MSC concentration at the wound site in initial healing stages [144]. As for fractured bone, increased TNF- α levels led to a reduced MSC concentration in a cortical callus by about 25% [144]. It has also been observed in diabetic animals that TNF- α increases can increase osteoclast number and lead to premature resorption of callus cartilage compared to normoglycemic animals [11].

As seen, DM impairs the initial cytokine and MSC recruitment phase, which delays soft callus formation and transitions to the repair phase. The soft callus is formed by periosteal progenitors that are recruited to the inflammatory site. It has been shown that DM impairs the migration of these progenitors and their differentiation, resulting in impaired callus formation and osteoblast recruitment [11]. Furthermore, the already existing balance of osteoblast and osteoclast function is disrupted by DM, as it creates a chronic hyperglycemic, inflammatory, and oxidative state that leads to the generation of disruptive ROS [11].

Overall, osteoblast recruitment and differentiation are impaired, existing osteocyte functions are impaired, callus and collagen development becomes abnormal, and the healing cascade is abnormal. Failure to appropriately resolve the inflammatory phase delays progression to reparative healing, establishing the foundation for subsequent vascular and structural deficiencies that can be observed clinically.

4.3.2. Impaired Angiogenesis and Callus Formation

Successful resolution of the inflammatory cascade normally initiates angiogenesis and reparative callus formation. In a fracture, vascular supply to long bones is compromised, and new blood vessels must proliferate from surrounding vessels (angiogenesis) to give the stable supply of oxygen, nutrients, progenitor cells, and growth factors that healing fractures need. Vascular endothelial growth factor (VEGF), and more specifically VEGF-A, is the main factor of angiogenesis regulation and endothelial cell growth. VEGF has also

been shown to induce osteoblast precursor proliferation and differentiation, as well as chemotaxis of MSCs. VEGF levels are increased locally and systemically during healing, and the mentioned roles of VEGF help explain why it is involved in many steps within the fracture healing sequence. It is initially concentrated in the hematoma, and it is also involved with the final bone turnover/remodeling phase upon healing completion [145].

Diabetes is known to impair angiogenesis via endothelial dysfunction, impaired VEGF signaling, and microvascular disease. Endothelial progenitor cells are reduced in both T1DM and T2DM and in animal models, and angiogenesis is hampered. Part of the reasoning lies in the elevated TNF- α levels in DM, as TNF- α has been linked to suppressed VEGF-A function. Furthermore, DM has been shown to result in reduced hypertrophic chondrocytes that express VEGF-A by 50% compared to normoglycemic fractures, so both the availability and function of VEGF-A are impaired by elevated TNF- α and diabetes [146]. This impaired angiogenesis then leads to an under-perfused, weaker, and fibrotic callus during fracture repair in diabetes. Chronic diabetes and microangiopathy of surrounding small vessels also contribute to reduced perfusion to the wound, and overall blood supply deficits have been shown to increase impaired fracture healing incidence from 10–15% to 46% [147].

Within the improper callus that forms, DM not only reduces vascularity, but it also alters MSC fate, limiting the pool of osteogenic progenitors available for callus formation and fracture healing. This was demonstrated in a study that used a murine model of T2DM and showed T2DM to be associated with increased callus adiposity. This meant that MSC fate was shifted to the adipocyte path rather than the osteoblast lineage more often, possibly because of PPAR γ (adipogenesis regulator) upregulation, resulting in fewer osteoblasts and delayed fracture healing [148]. These findings are clinically significant when considering their relation to the pathophysiology of nonunion as well.

Dysregulation of angiogenesis, callus formation, MSC recruitment, and osteoblast differentiation are key factors in nonunion that require further interventions [149]. This makes them key factors to consider in the orthopedic field to assess fracture healing timelines and when having discussions about future complications and/or needs for reoperation (or operation in external fixation). More specific to our discussion, the impact of DM on these regulators of fracture healing is important to consider in the orthopedic world when assessing fracture timelines and nonunion risk.

These biological interactions and abnormalities have measurable clinical consequences noted in the literature. Multiple systematic reviews demonstrate increased rates of delayed union, nonunion, infection, malunion, and reoperation among diabetic patients undergoing fracture treatment. An example of one was published in 2018 that found diabetes to be linked with the previously mentioned fracture complications in lower extremity fractures [150]. An even more comprehensive review in 2020 linked diabetes with impaired fracture healing in more detailed subgroups, especially within lower extremity fractures, short bones, and osteoporosis-unrelated fractures. This review calls for more clinical studies with adequate sample sizes, but the impact of diabetes on fracture healing in most patients has been extensively noted [10]. Impaired vascularization and callus maturation provide a mechanistic explanation for the increased rates of delayed union and nonunion observed clinically in diabetic populations. The interconnected molecular, cellular, and clinical mechanisms through which diabetes impairs fracture healing and orthopedic outcomes are summarized in Figure 3.

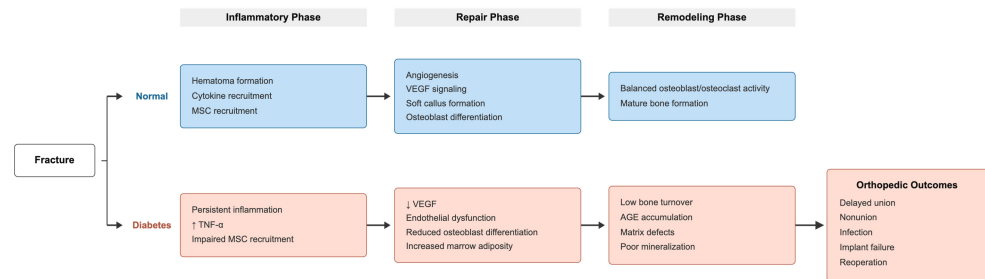


Figure 3. Mechanisms Contributing to Impaired Fracture Healing in Diabetes. Schematic representation of the sequential phases of fracture healing and the biological alterations that occur under diabetic conditions. Each healing phase is disrupted by distinct pathological mechanisms that collectively impair bone repair and ultimately contribute to delayed union, nonunion, infection, implant failure, and reoperation.

4.4. Clinical Implications for Surgical Planning

Recognition of these contributing factors to skeletal fragility in diabetes holds clinical implications and should influence risk assessment, perioperative counseling, and fracture management strategies when undergoing surgical counseling and planning. While diabetes affects bone quality, remodeling, and healing capacity, traditional risk assessment strategies underestimate skeletal risk.

DXA and FRAX alone are incapable of assessing total orthopedic risk, and surgeons should recognize the other microarchitectural factors of diabetic bone disease preoperatively [3]. Recognition of these factors will mean incorporating clinical factors, glycemic status, fracture history, and emerging indicators of bone quality into preoperative assessments [6,139]. BMD has been shown to not be sufficient alone, especially in T2DM, when assessing fracture risk. Then, after a fracture, DM modifies the metabolic environment, influencing the fracture site and healing outcomes. For these reasons, usual medical history-taking holds great orthopedic clinical significance when accounting for diabetes in surgical planning.

Some diabetes factors may be modifiable before surgery and could hold promise for influencing healing outcomes in the future. For example, managing a patient's hyperglycemia/HbA1c could improve the inflammation issue discussed in Section 4.3.1 and help manage vascular disease/angiogenesis impairment in fracture healing [151]. Using diabetes as a preoperative modifiable factor has already been noted by a study as a means of improving surgical site infection risk, and this could be extended to improve overall surgical outcomes for diabetic patients [152].

Diabetes and diabetic skeletal fragility should also be considered by clinicians when considering surgical strategies and postoperative expectations. Factors to consider include hyperglycemia, neuropathy, peripheral artery occlusion, and unstable bone, which can lead to postoperative complications. One study showed that ankle fractures in diabetic patients must be treated with these factors in mind, as they often lead to poorer outcomes, fixation failures, delayed union, and nonunion. The study went on to explain why diabetes is important to discuss in surgical planning, why we need stronger constructs for unstable diabetic bone, and why closer postoperative surveillance in diabetic patients is imperative [153].

Postoperative surveillance should be accompanied by counseling regarding realistic healing expectations and complication risks associated with diabetes. Patients may understand how their diabetes affects their glucose, but they may not realize its impact on their bones and fracture risk/recovery. Physicians should be able to discuss delayed healing, nonunion risk, infection risk, and prolonged recovery timelines with patients. This understanding is vital when it comes to management and truly informed consent.

As we have covered, current tools remain imperfect in allowing physicians to adequately assess and convey risks associated with diabetic bone disease. Bone quality biomarkers, genetic markers, and advanced imaging techniques are emerging, paving the future for potential precision-medicine approaches. These approaches will recognize diabetic bone disease's important implications for orthopedic practice. Impaired bone quality, altered remodeling, and delayed repair when considered together imply that traditional approaches for fracture-risk assessment may underestimate skeletal vulnerability in diabetic patients. Precision-medicine approaches that incorporate metabolic status, bone-quality measures, and individualized risk factors into surgical planning may improve patient counseling, perioperative optimization, and long-term musculoskeletal outcomes.

5. Orthopedic Implications and Emerging Therapeutic Strategies

The cellular, molecular, endocrine, and structural abnormalities discussed throughout Sections 2–4 ultimately converge at the point most relevant to orthopedic practice: impaired skeletal repair and poorer surgical outcomes. Chronic hyperglycemia, oxidative stress, advanced glycation end-product accumulation, dysregulated bone remodeling, and deterioration of bone quality collectively reduce the skeleton's ability to respond to injury, while conventional fracture-risk assessment tools frequently underestimate this vulnerability. As a consequence, patients with diabetes experience disproportionately high rates of delayed fracture healing, postoperative complications, and reconstructive failure despite often presenting with preserved BMD. These observations have shifted attention toward strategies that extend past glycemic control alone, including optimization of perioperative management, selection of diabetes therapies with favorable skeletal effects, precision risk stratification, and regenerative approaches aimed at restoring bone repair and improving orthopedic outcomes.

5.1. Orthopedic Surgical Outcomes in Diabetic Patients

Fracture healing represents one of the most significant orthopedic complications associated with both type 1 and type 2 diabetes mellitus [10]. As discussed throughout Sections 2–4, chronic hyperglycemia disrupts the biological and mechanical processes required for successful skeletal repair, leading to impaired bone remodeling, delayed regeneration, and compromised tissue integration. These alterations translate clinically into higher rates of fracture-related complications, particularly involving the lower extremities [10]. While malunion occurs approximately six times more frequently in diabetic populations than in healthy controls, the incidence of nonunion is more variable and appears to depend upon fracture location and patient characteristics [150]. Lower extremity fractures, particularly those involving the foot and ankle, demonstrate the greatest susceptibility to impaired healing, with insulin dependence further increasing the likelihood of postoperative complications [10,150]. Furthermore, insulin dependence can heighten the risk for complications in lower extremity fracture healing [150]. Consistent with these findings, analyses of ankle fracture fixation have shown that insulin-dependent diabetes, particularly when glycemic control is poor, is associated with significantly higher complication rates following surgical fixation [150].

Postoperative infection likewise represents a major contributor to poor orthopedic outcomes in diabetic patients. Infection rates following fracture fixation are approximately threefold higher than those observed in non-diabetic populations, frequently presenting as wound-edge necrosis, tissue dehiscence, or deep surgical site infection [150]. Deep infections often require additional surgical intervention and substantially increase the likelihood of reoperation. Collectively, impaired fracture healing and postoperative infection

contribute to greater rates of orthopedic complications following fixation procedures in patients with diabetes.

Orthopedic arthrodesis demonstrates similar challenges, particularly in the lower extremities where diabetes-related neuropathy and vascular compromise further impair skeletal repair. Successful arthrodesis depends upon coordinated bone formation, remodeling, and osseous fusion, all of which are adversely affected by diabetes mellitus. Clinical studies consistently identify diabetes and peripheral neuropathy as important risk factors for nonunion following ankle arthrodesis procedures, although the magnitude of risk varies across individual studies [13,154]. Even in studies where diabetes was not independently associated with nonunion following tibiototalcanal arthrodesis (TTCA), diabetic patients continued to experience higher rates of superficial infection, increasing the likelihood of revision procedures [13]. Collectively, these findings emphasize the importance of optimizing glycemic control before arthrodesis to improve the probability of successful fusion.

Further evidence supports the relationship between metabolic control and arthrodesis outcomes. Approximately one-quarter of diabetic patients experience at least one bone-healing complication following foot and ankle arthrodesis, with elevated hemoglobin A1c levels consistently associated with poorer healing outcomes [154]. Similarly, structural TTCA allograft procedures have demonstrated markedly reduced fusion success in diabetic patients [154]. Additional factors, including smoking history, peripheral ulceration, and chronic kidney disease, further contribute to impaired fusion; however, diabetes and peripheral neuropathy remain among the strongest predictors of unsuccessful arthrodesis [13,154].

While joint arthroplasty depends less upon fracture healing and more upon reducing infections, diabetes remains an important factor in a successful operation. Studies controlling for BMI and perioperative hyperglycemia demonstrate significant associations between elevated glucose levels and surgical site infection following arthroplasty [152]. Likewise, patients with poorly controlled diabetes (HbA1c > 7%) experience higher rates of wound complications, prolonged hospitalization, and inferior postoperative outcomes than patients with better glycemic control [155]. Although optimization of diabetes reduces surgical risk, complication rates remain elevated relative to non-diabetic populations. Thus, there should be emphasis on the continued importance of careful perioperative management.

The relationship between long-term glycemic control and postoperative infection has also been demonstrated in patients undergoing major noncardiac surgery. Higher pre-operative HbA1c concentrations are consistently associated with increased postoperative infection, whereas patients with well-controlled diabetes (HbA1c < 7%) experience lower rates of infectious complications [156]. At the highest levels of hyperglycemia, nearly one-third of patients with HbA1c values exceeding 11.5% developed postoperative infection [156]. These findings further support glycemic optimization as a practical strategy for improving orthopedic surgical outcomes.

Successful orthopedic reconstruction depends upon adequate bone healing, vascular perfusion, and biological integration, all of which are adversely affected by diabetes mellitus [157]. Autologous bone grafting remains a common reconstructive strategy; however, donor-site morbidity, limited graft availability, and incomplete vascularization continue to limit its effectiveness [158]. Hyperglycemic conditions further exacerbate these limitations, increasing the likelihood of malunion, nonunion, and reconstructive failure following complex orthopedic procedures [157,158].

Several clinical factors influence orthopedic outcomes in diabetic patients, with HbA1c remaining among the strongest predictors of postoperative success. Peripheral neuropathy, peripheral vascular disease, chronic kidney disease, prior ulceration, and lower extremity fracture location also contribute to impaired healing and increased surgical complications.

Despite the identification of these risk factors, considerable variability in patient outcomes remains. Consequently, therapeutic strategies that improve metabolic control while directly enhancing bone remodeling and fracture repair represent an important area of ongoing investigation and provide the rationale for the emerging treatment approaches discussed in the following section.

5.2. Effects of Antidiabetic Therapies on Skeletal Health

Antidiabetic therapies influence skeletal health through mechanisms that extend beyond glycemic control. Although improving glucose regulation generally benefits bone remodeling and fracture healing, individual drug classes exert distinct effects on osteoblast function, bone turnover, and skeletal integrity. Consequently, medication selection may influence fracture risk and orthopedic outcomes independent of metabolic control alone.

Metformin has consistently demonstrated favorable effects on skeletal health through activation of AMP-activated protein kinase (AMPK), increased RUNX2 transcription, and enhanced osteoblast differentiation [159]. These molecular effects have translated into improved clinical outcomes, with cohort studies demonstrating higher BMD at the femoral neck, lumbar spine, and total hip among patients receiving metformin compared with untreated individuals [160]. Similarly, women treated with metformin were less likely to develop osteoporosis [160]. Furthermore, a meta-analysis identified a significant inverse association between metformin use and fracture risk [161]. These findings suggest that metformin may provide skeletal benefits beyond glucose regulation.

In contrast, thiazolidinediones (TZDs) have consistently been associated with adverse skeletal outcomes. As discussed previously, activation of PPAR γ shifts MSC differentiation toward adipogenesis and away from osteoblastogenesis, ultimately reducing bone formation. Clinical studies support these mechanistic observations, with long-term TZD therapy associated with reduced BMD and increased fracture risk, particularly among women with type 2 diabetes mellitus [162]. A subsequent meta-analysis further demonstrated increased risks of fracture, weight gain, congestive heart failure, and bladder cancer during prolonged TZD treatment [163]. Although TZDs remain effective glucose-lowering agents, their unfavorable skeletal profile should be considered when selecting therapy for patients at increased risk of fracture.

The effects of insulin therapy on skeletal health remain less clearly defined. Experimental studies have demonstrated improvements in trabecular microarchitecture, serum calcium, and osteogenic markers following insulin treatment in animal models of both type 1 and type 2 diabetes [164]. However, these findings have not been consistently reproduced in human studies, with clinical investigations reporting variable associations between circulating insulin levels and BMD [164]. The heterogeneous nature of these findings suggests that disease severity, duration of diabetes, and patient-specific characteristics may influence the skeletal response to insulin therapy, highlighting the need for further clinical investigation.

Sodium-glucose cotransporter-2 inhibitors (SGLT2is) have likewise demonstrated mixed skeletal effects. Early investigations suggested potential alterations in bone turnover, bone strength, and microarchitecture without a corresponding increase in fracture risk [165]. Although initial studies questioned whether glucose lowering might indirectly increase falls and fracture risk, subsequent investigations failed to support a harmful skeletal effect and instead recommended continued evaluation [166]. More recent evidence has been encouraging, with a 2025 meta-analysis demonstrating reduced fracture risk among patients receiving SGLT2 inhibitors compared with other antidiabetic therapies [167]. These findings suggest that concerns regarding adverse skeletal effects may have been overstated, although continued long-term evaluation remains warranted.

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) have emerged as another promising class of antidiabetic medications with potential musculoskeletal benefits. In addition to improving glycemic control, GLP-1RAs promote weight loss through increased satiety and delayed gastric emptying, thereby reducing mechanical loading across weight-bearing joints [168]. Current clinical evidence has not demonstrated an increased risk of fracture and suggests that GLP-1RAs may modestly improve BMD [169]. Nevertheless, long-term skeletal effects remain uncertain, as experimental studies have reported alterations in myogenic pathways that could contribute to sarcopenia during prolonged treatment [168]. Additional clinical and translational studies are therefore needed before definitive conclusions regarding their effects on skeletal health can be established.

Bariatric and metabolic surgery represents another setting in which metabolic intervention intersects with skeletal physiology. In patients with T2DM, these procedures can produce substantial improvements in metabolic control, but their skeletal effects may be less favorable. In a randomized trial of patients with T2DM, both Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy were associated with reductions in bone mineral content and hip BMD at two years compared with intensive medical therapy, despite calcium and vitamin D supplementation [170].

Longer-term skeletal effects may also differ by procedure. In a cross-sectional analysis performed a mean of 6.8 years after surgery, BMD was lower after RYGB than after sleeve gastrectomy despite similar weight loss and body composition, while biochemical differences between groups were consistent with persistent procedure-specific effects on mineral metabolism [171]. Weight and lean-mass loss may contribute to these skeletal effects, as changes in hip BMD following surgery were strongly associated with both weight loss and reductions in lean mass [170]. Therefore, although bariatric surgery can provide substantial metabolic benefits in T2DM, its potential effects on skeletal health should also be considered.

Although several antidiabetic medications demonstrate favorable skeletal effects, no single therapy consistently optimizes both glycemic control and musculoskeletal outcomes across all patient populations. Consequently, treatment selection should consider fracture risk, osteoporosis, peripheral neuropathy, delayed healing, and planned orthopedic procedures in addition to traditional metabolic endpoints. At present, evidence describing the effects of antidiabetic medications on fracture healing remains considerably more limited than data regarding fracture risk or BMD. Future studies should therefore focus on determining how medication-specific skeletal effects influence bone regeneration, postoperative recovery, and orthopedic outcomes. Such efforts may ultimately support precision medicine strategies that integrate biomarkers, molecular profiling, and individualized risk assessment to optimize both diabetic management and skeletal health.

5.3. Precision Medicine and Future Orthopedic Management

Diabetic bone disease demonstrates considerable heterogeneity among patients, resulting in substantial variability in fracture risk and orthopedic outcomes despite similar clinical characteristics. Differences in BMD, microarchitecture, skeletal fragility, and healing potential have been observed both within and between diabetes subtypes [172]. Current fracture-risk assessment tools, including DXA and FRAX, frequently fail to capture these patient-specific differences and may underestimate skeletal fragility in diabetes [3,7,173]. Consequently, more individualized approaches to risk assessment are needed to better identify patients at greatest risk for fracture, delayed healing, and postoperative complications.

Advanced imaging modalities and biochemical markers provide opportunities to improve patient-specific assessment of diabetic bone disease. TBS evaluates bone microarchitecture through gray-level texture analysis and has demonstrated reduced values in

patients with type 2 diabetes despite preserved or elevated BMD [128,129]. Likewise, HR-pQCT provides detailed assessment of cortical and trabecular microarchitecture that cannot be obtained using conventional DXA [128]. When combined with biochemical markers, clinical variables, fracture history, peripheral neuropathy, and vascular disease, these approaches provide a more comprehensive evaluation of skeletal fragility than conventional imaging alone.

Genetic and epigenetic profiling may further improve individualized risk assessment. GWASs have identified susceptibility loci associated with BMD and skeletal health, providing the foundation for polygenic risk scores and genetic susceptibility profiling in diabetic bone disease [100]. Although these technologies remain investigational, they may eventually complement advanced imaging and biomarker analysis to improve fracture-risk prediction and guide individualized treatment strategies. Additional clinical validation is required before these approaches can be routinely incorporated into orthopedic practice.

Despite the limitations of current precision medicine technologies, individualized management can already be incorporated into clinical decision-making. Patients with well-controlled diabetes frequently achieve orthopedic outcomes comparable to those of non-diabetic individuals, emphasizing the importance of optimizing modifiable risk factors before surgery [14]. Clinical variables such as HbA1c, peripheral neuropathy, vascular disease, and fracture location may influence operative timing, fixation strategy, perioperative optimization, and patient selection. Similarly, medical optimization with therapies such as metformin and, when appropriate, GLP-1 receptor agonists may improve glycemic control while providing favorable musculoskeletal effects that support surgical recovery [174].

Although many precision medicine strategies remain under active investigation, continued integration of advanced imaging, circulating biomarkers, genetic profiling, and individualized clinical risk factors has the potential to improve orthopedic management of diabetic bone disease. Future studies should focus on validating these technologies, refining patient selection, and determining how individualized treatment strategies can improve fracture healing, reduce complications, and optimize long-term orthopedic outcomes.

5.4. Emerging Orthobiologic and Regenerative Approaches

Despite advances in glycemic management and perioperative optimization, impaired bone regeneration remains a major challenge in diabetic patients. Persistent alterations in osteoblast activity, angiogenesis, inflammation, and MSC function often limit endogenous repair despite adequate metabolic control. Consequently, regenerative strategies are increasingly being developed to directly target the biological mechanisms responsible for delayed bone healing and skeletal fragility.

Anabolic therapies have demonstrated encouraging results for improving bone formation and skeletal repair. Teriparatide stimulates osteoblast activity through recombinant parathyroid hormone signaling and has consistently improved bone formation and delayed fracture healing in experimental models [175,176]. Although human studies remain limited, reductions in fracture union time and improvements in pain have been reported following treatment, suggesting potential clinical benefit [175,176]. Likewise, romosozumab has demonstrated significant improvements in BMD at the lumbar spine, femoral neck, and total hip, while combination therapy with alendronate has improved trabecular bone score in patients with type 2 diabetes mellitus [162,163]. Although these findings support anabolic therapy as one of the most clinically advanced regenerative approaches, additional randomized clinical trials are needed to establish their role in diabetic fracture healing.

Orthobiologic therapies provide an alternative strategy by enhancing the biological environment surrounding skeletal repair. Growth factors including vascular endothelial

growth factor (VEGF), platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), bone morphogenetic proteins (BMPs), transforming growth factor- β (TGF- β), and insulin-like growth factors (IGFs) stimulate angiogenesis, MSC recruitment, and osteoblast differentiation during bone regeneration [177]. Platelet-rich plasma (PRP), platelet-rich fibrin (PRF), and bone marrow aspirate (BMA) concentrate many of these biologically active factors and are frequently combined with biomaterial scaffolds to improve local delivery while providing mechanical support [177,178]. Although diabetic-specific clinical evidence remains limited, these approaches may help overcome the impaired regenerative environment associated with diabetes.

MSC therapies directly target one of the fundamental mechanisms of diabetic bone disease by restoring osteogenic potential. As discussed in Section 3.2, diabetes promotes adipogenic differentiation at the expense of osteoblastogenesis, contributing to impaired bone formation. Experimental strategies aimed at enhancing Wnt signaling, increasing osteogenic growth factors, reducing oxidative stress and AGEs, or modifying osteogenic gene expression have demonstrated improved osteogenesis and angiogenesis in preclinical models [179,180]. However, challenges related to cell survival, immune compatibility, manufacturing complexity, and regulatory approval continue to limit widespread clinical translation [181].

Extracellular vesicles (EVs) have emerged as a promising cell-free alternative that may overcome many limitations associated with stem cell therapy. EVs transport proteins, lipids, nucleic acids, and other signaling molecules capable of regulating inflammation, angiogenesis, osteogenesis, and bone remodeling [182]. Experimental studies have demonstrated improved bone regeneration using macrophage-derived EVs, including hydrogel-delivered M2EV@CaP constructs that enhanced bone repair in diabetic animal models [182,183]. While these findings remain largely preclinical, EV-based therapies may provide a more practical and scalable regenerative platform than cellular therapies.

Although regenerative therapies remain largely investigational, accumulating evidence suggests that future management of diabetic bone disease will likely rely on combination approaches rather than a single intervention. Integration of anabolic therapies, orthobiologics, stem cell or extracellular vesicle technologies, and precision medicine strategies may improve fracture healing, bone regeneration, and long-term orthopedic outcomes. Future clinical studies should focus on validating these approaches in diabetic populations while identifying the patients most likely to benefit from individualized regenerative therapies.

6. Conclusions and Future Directions

Diabetic bone disease is increasingly recognized as a multifactorial skeletal disorder that extends beyond alterations in BMD alone. Chronic hyperglycemia disrupts bone remodeling through coordinated effects on osteoblasts, osteoclasts, osteocytes, the extracellular matrix, and endocrine signaling networks, while oxidative stress, advanced glycation end-product accumulation, impaired insulin and IGF-1 signaling, chronic inflammation, and genetic and epigenetic dysregulation further compromise skeletal homeostasis. Consequently, patients with diabetes experience increased skeletal fragility, delayed fracture healing, and poorer orthopedic outcomes despite frequently maintaining normal or elevated BMD, particularly in type 2 diabetes. Across these mechanisms, however, a consistent pattern emerges: diabetic bone disease cannot be fully understood through alterations in bone mass alone but instead reflects complex interactions between metabolism, bone biology, and tissue repair.

Current clinical management remains limited by the inability of conventional diagnostic tools to fully characterize this complexity. Although DXA and FRAX remain the

foundation of fracture-risk assessment, both frequently underestimate skeletal fragility because they inadequately capture alterations in bone quality and microarchitecture. Similarly, traditional bone turnover markers provide only limited insight into the low-turnover skeletal phenotype characteristic of many patients with diabetes. Successful orthopedic management therefore depends not only on optimizing glycemic control, but also on integrating patient-specific factors including neuropathy, vascular disease, fracture location, and overall metabolic status into clinical decision making.

Several priorities follow from this review. Advanced imaging modalities, biochemical biomarkers, and genetic and epigenetic profiling may improve individualized risk assessment beyond conventional clinical evaluation, while continued investigation of anabolic therapies, orthobiologics, MSC-based therapies, extracellular vesicles, and tissue-engineered approaches offers promising opportunities to restore impaired skeletal repair. However, many of these strategies remain investigational, and greater emphasis should be placed on prospective clinical studies that evaluate fracture healing and orthopedic outcomes in diabetic populations rather than BMD alone. Likewise, identifying biomarkers that predict fracture healing and validating precision medicine approaches will be important for translating these emerging technologies into routine orthopedic practice.

This review integrates the molecular mechanisms underlying diabetic bone disease with their clinical and orthopedic consequences, highlighting the interconnected relationships among metabolic dysfunction, skeletal fragility, fracture healing, and regenerative medicine. Although variability in experimental models, patient populations, and study design continues to limit direct comparison across studies, continued collaboration among orthopedic surgeons, endocrinologists, and translational scientists will be essential for advancing the field. Improving our understanding of diabetic bone disease across molecular, clinical, and regenerative disciplines has the potential to support more accurate risk stratification, improve fracture management, and facilitate the development of targeted therapies that enhance skeletal health and orthopedic outcomes in patients with diabetes.

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Abbreviations

The following abbreviations are used in this manuscript:

BMD	Bone Mineral Density
DXA	Dual-Energy X-ray Absorptiometry
ROS	Reactive Oxygen Species
AGEs	Advanced Glycation End Products
P1NP	Procollagen Type 1 N-Terminal Propeptide
CTX	Carboxyl-Terminal Cross-Linking Telopeptide of Type 1 Collagen
SASP	Senescence-Associated Secretory Phenotype
LCN	Lacunocanalicular Network
LOX	Lysyl Oxidase
GIP	Glucose-Dependent Insulinotropic Polypeptide
GLP-1	Glucagon-Like Peptide-1
BMAT	Bone Marrow Adipose Tissue
MSC	Mesenchymal Stem Cell
GWAS	Genome-Wide Association Studies
SNPs	Single-Nucleotide Polymorphisms
FRAX	Fracture Risk Assessment Tool
T2DM	Type 2 Diabetes Mellitus
T1DM	Type 1 Diabetes Mellitus
DM	Diabetes Mellitus
BMI	Body Mass Index
HR-pQCT	High-Resolution Peripheral Quantitative Computed Tomography
TBS	Trabecular Bone Score
NTX	Amino-Terminal Cross-Linking Telopeptide of Type 1 Collagen
TRACP-5b	Tartrate-Resistant Acid Phosphatase 5b
PYD	Pyridinoline
DPD	Deoxypyridinoline
P1CP	Procollagen Type 1 C-Terminal Propeptide
PTH	Parathyroid Hormone
eGFR	Estimated Glomerular Filtration Rate
BTMs	Bone Turnover Markers
CML	Carboxymethyl-Lysine
HbA1c	Hemoglobin A1c
TTCA	Tibiototalcaneal Arthrodesis
TZDs	Thiazolidinediones
SGLT2is	Sodium-Glucose Cotransporter-2 Inhibitors
GLP-1RAs	Glucagon-Like Peptide-1 Receptor Agonists
PRP	Platelet-Rich Plasma
PRF	Platelet-Rich Fibrin
BMA	Bone Marrow Aspirate
EVs	Extracellular Vesicles

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