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REVIEW ARTICLE

Diabetes and Bone Health: A Comprehensive Review of Impacts and Mechanisms

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ABSTRACT

Diabetic bone disease, a form of secondary osteoporosis, is characterised by reduced bone strength and increased fracture risk, particularly in patients with type 2 diabetes (T2D). Over 35% of T2D patients experience bone loss, with approximately 20% meeting diagnostic criteria for osteoporosis. This review highlights the complex mechanisms underlying diabetic bone disease, emphasising the need to reduce fracture risk and improve clinical outcomes. Key factors such as hyperglycemia, insulin resistance, insulin-like growth factors (IGFs), advanced glycation end products (AGEs), and proinflammatory cytokines disrupt bone turnover by impairing osteoblast and osteoclast function, leading to imbalanced bone formation and resorption. We explore the role of bone turnover and mineralisation in both cortical and trabecular bone, and the impact of microvascular complications on bone microarchitecture. Gut hormones, including Glucagon-like peptide-1 (GLP-1), Glucose-dependent insulinotropic polypeptide (GIP), and Parathyroid hormone (PTH), and the gut microbiota also play crucial roles in the pathogenesis of diabetic bone disease. Specific bacterial species, such as *Akkermansia muciniphila* and *Bacteroides fragilis*, are implicated in modulating the gut-bone axis through short-chain fatty acids (SCFAs) and other signalling pathways. These changes, along with altered gut hormone responses, affect bone density, microstructure, and material properties. Despite normal or increased bone mineral density (BMD) in some T2D patients, the material quality of bone is compromised, leading to greater fragility. This review integrates current knowledge of molecular, hormonal, and microbial interactions that contribute to diabetic bone disease, offering insights into potential therapeutic strategies and improving patient care.

1 | Introduction

As people age and adopt new lifestyle habits and dietary changes, diabetes mellitus has become the third most significant non-communicable disease after cardiovascular diseases and cancer. Diabetes mellitus comprises a group of metabolic disorders characterised by persistent hyperglycemia caused by various aetiologies, leading to insufficient insulin secretion and impaired insulin action [1]. According to the International Diabetes Federation, the number of individuals with diabetes mellitus worldwide reached 530 million in 2021, with projections estimating this figure will surpass 780 million by 2045 [2]. The chronic nature of diabetes mellitus can damage multiple organs and systems throughout the body, resulting in numerous complications. Besides the commonly known complications such as diabetic retinopathy, nephropathy, and cardiovascular disease, diabetes mellitus can also impact the skeletal system, leading to bone loss and osteoporosis (Figure 1) [3]. Diabetes negatively

Prabhat Upadhyay and Sudhir Kumar contributed equally.

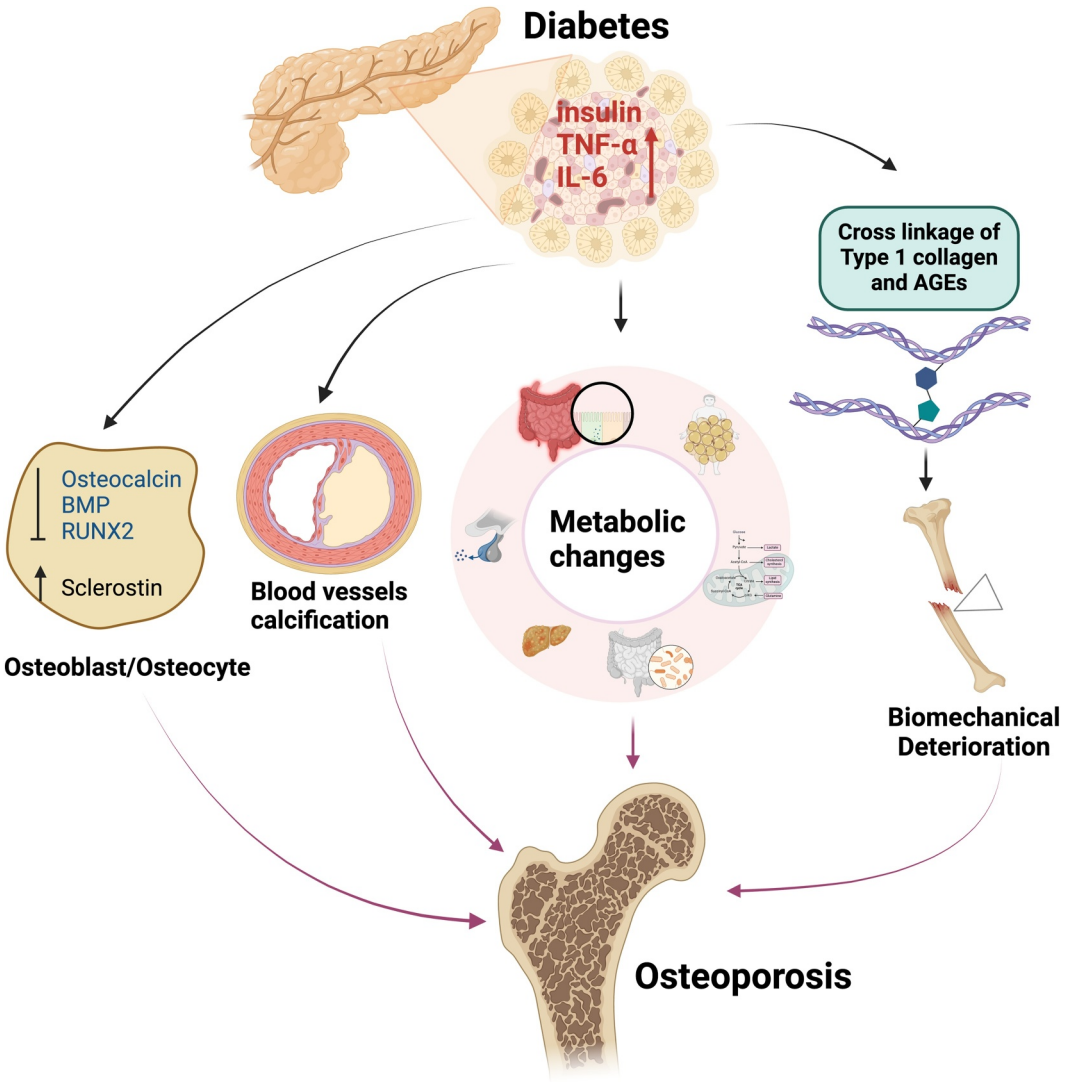

FIGURE 1 | Key factors involved in diabetic bone disease. This figure illustrates the multifactorial mechanisms contributing to diabetic bone disease and osteoporosis (*Created with BioRender.com*). Metabolic changes: Elevated insulin levels, hyperglycemia, and increased proinflammatory markers drive systemic metabolic alterations. Dysbiosis of the gut microbiota, along with imbalanced gut hormones (e.g., GLP-1, GIP), adipocyte deposition, and fatty liver, impairs bone turnover. These factors collectively lead to biomechanical deterioration, ultimately increasing osteoporosis risk. Diabetes also directly inhibits osteoblast proliferation and differentiation and increasing the blood vessel calcification, which leads to osteoporosis. Microvascular and macrovascular complications: Diabetes-induced complications such as nephropathy, retinopathy, neuropathy, impaired wound healing, and cardiovascular issues contribute to blood vessel calcification, which exacerbates trabecular bone loss and leads to osteoporosis. Biomechanical deterioration: Diabetes influences bone biochemistry through the accumulation of advanced glycation end products (AGEs) and alterations in collagen type 1, which compromise bone integrity. Additionally, ageing further impairs bone material properties. Molecular pathways: Hyperglycemia inhibits osteocalcin, RUNX2 (Runt-related transcription factor 2), and bone morphogenetic protein (BMP) expression while increasing sclerostin levels, disrupting bone formation and microarchitecture, leading to weakened bones and increased osteoporosis susceptibility.

impacts bones, increasing fracture risk. The mechanisms underlying bone alterations differ significantly between type 1 and type 2 diabetes. Type 1 diabetes (T1D) occurs when the pancreas does not produce insulin because the body's immune system attacks the islet cells in the pancreas that make insulin and T1D more severely affects bones through a simpler pathophysiological mechanism involving reduced bone mineral density (BMD). T1D can develop at any age; typically, detection age is adolescence, a period of rapid skeletal growth, resulting in compromised bone health at an earlier age and more severe consequences with ageing [4]. In contrast, the incidence and prevalence of T1D are lower than those of T2D. In T2D, the pancreas makes less insulin than used to, and the body becomes resistant to insulin [4]. The adverse effects of T2D on bone health have been recognized more recently. The pathophysiology of T2D's impact on bones is more complex, particularly because T2D is often associated with obesity, which can also negatively affect bone health. Additionally, BMD is variably elevated in T2D, an effect that might be expected to increase bone strength [5].

Limited data are available on managing bone fragility in diabetic patients. Overall, there are few differences from the standard

treatment of bone fragility. Type 1 and type 2 diabetes mellitus affect millions globally and are characterised by hyperglycemia and complications that negatively impact patients' quality of life and impose a significant economic burden on society. Thus, the diagnosis, treatment, and prevention of diabetes and its complications are crucial. Traditional diabetes complications include microvascular complications (retinopathy, nephropathy, and neuropathy) and macrovascular complications (such as cardiovascular disease) [6]. Over the last 50 years, it has become evident that diabetes also affects bone health, increasing the risk of fractures. Diabetic bone disease arises from complex mechanisms that impair bone quality [7]. Additionally, an increased risk of falls in diabetic patients and potential side effects of diabetes treatment may further elevate fracture risk. Traditional fracture predictors like BMD and the fracture risk assessment (FRAX) tool often underestimate fracture risk in diabetes, reinforcing the notion that bone quality is compromised by the disease. Osteoporosis is a systemic bone disease marked by reduced bone mass and deterioration of bone microarchitecture, leading to increased bone fragility and a higher susceptibility to fractures. According to dual-energy X-ray absorptiometry (DXA) criteria, osteoporosis is defined as a BMD value at the femoral neck that is 2.5 standard deviations or more below the young female adult mean (T-score ≤ -2.5 SD) [8]. Osteoporosis resulting from diabetes mellitus, referred to as diabetic bone disease, is a chronic condition that heightens bone fragility and fracture risk due to decreased bone mass and damage to bone tissue microstructure induced by diabetes mellitus. Diabetic bone disease is a secondary form of osteoporosis that predisposes patients to chronic bone pain and motor dysfunction, with a higher risk of disability and fractures compared with primary osteoporosis [9]. A survey of patients with T2DM indicated that over 35% of patients experienced bone loss, with approximately 20% meeting the diagnostic criteria for osteoporosis [10]. This review provides a comprehensive overview of current knowledge on diabetic bone disease and fracture risk in diabetic patients, covering epidemiology and underlying mechanisms in managing bone disease.

2 | Pathophysiology of Diabetic Bone Disease

Diabetic bone disease is characterised by altered bone metabolism and increased fracture risk due to several underlying mechanisms. These include insulin and insulin-like growth factor 1 (IGF-1) deficiencies, hyperglycemia and the accumulation of advanced glycation end products (AGEs), and the effects of pro-inflammatory cytokines and oxidative stress (Figure 2). High glucose in circulation elevates advanced glycation end products (AGEs) and oxidative stress, which stimulate osteocytes to produce sclerostin [11]. Sclerostin is a Wnt signalling inhibitor which ultimately inhibits bone formation [12]. Diabetes inhibits osteoblast differentiation from mesenchymal stem cells, diverting them towards adipocyte formation via the PPARγ (Peroxisome proliferator-activated receptor) pathway, thereby increasing inflammation and oxidative stress [13]. An increase in key osteoclast markers such as RANKL (Receptor activator of nuclear factor-κB ligand)/OPG ratio, CTx, Trap5b (Tartrate-resistant acid phosphatase 5b), and NFATc1 (Nuclear factor of activated T cell) leads to high bone resorption. In contrast, osteoblast function is downregulated with decreased expression of RUNX2, Wnt signalling, osteocalcin, osteopontin, and BMP-2, inhibiting bone mineralisation [14, 15]. The Figure 2 demonstrates how diabetes-induced changes in osteoblast and osteoclast activity, along with increased oxidative stress and adipogenesis, contribute to defective bone remodelling, leading to compromised bone strength and increased risk of osteoporosis.

2.1 | Insulin and IGF-1 Deficiency

Insulin plays a crucial role in maintaining bone health, largely through its effects on osteoblasts—the cells responsible for bone formation. Osteoblasts have insulin receptors on their cell membranes, which, when activated, trigger intracellular signalling pathways that are essential for synthesising DNA, osteocalcin, and collagen. These components are vital for the formation of new bone tissue. Additionally, insulin enhances the expression of RUNX2, a key transcription factor that promotes the differentiation of osteoblasts and the maturation of the bone matrix [16]. This process is fundamental to the development and maintenance of strong, healthy bones. In the context of diabetes, the impact of insulin on bone health varies significantly between T1D and T2D. In T1D, an autoimmune condition leads to the destruction of pancreatic β-cells, which results in an absolute deficiency of insulin. This lack of insulin during adolescence, a critical period for bone development, results in insufficient bone mineralisation. As a result, individuals with T1D often experience low bone mineral density (BMD) throughout their lives. The lack of insulin not only hampers the bone-forming activities of osteoblasts but also fails to support the necessary expression of RUNX2, further contributing to poor bone health in these patients [17]. Consequently, people with T1D are at a higher risk of developing osteoporosis and other bone-related disorders as they age [18].

On the other hand, the relationship between insulin and bone health in T2D is more complex. Early in the course of T2D, patients typically experience insulin resistance, where their bodies do not effectively respond to insulin. To compensate, the pancreas produces more insulin, leading to a state of hyperinsulinemia. This increased insulin can initially enhance bone mineralisation, potentially leading to higher bone density in the early stages of T2D [19]. However, this apparent benefit is temporary. As T2D progresses, the pancreas's ability to produce insulin diminishes, leading to a decline in insulin levels. This reduction in insulin, coupled with the ongoing effects of insulin resistance, eventually results in decreased bone mineral density. Thus, patients with advanced T2D are also at an increased risk of bone fractures and other bone-related complications despite initially having higher bone mineralisation [20].

IGF-1 plays a crucial role in promoting osteoblast activity and bone matrix mineralisation. Diabetic patients, especially those with poorly controlled blood sugar levels, often exhibit significantly reduced levels of IGF-1, which is associated with diminished bone formation and an increased risk of fractures [21]. Structurally similar to insulin, IGF-1 has anabolic effects on osteoblasts, stimulating collagen synthesis and promoting

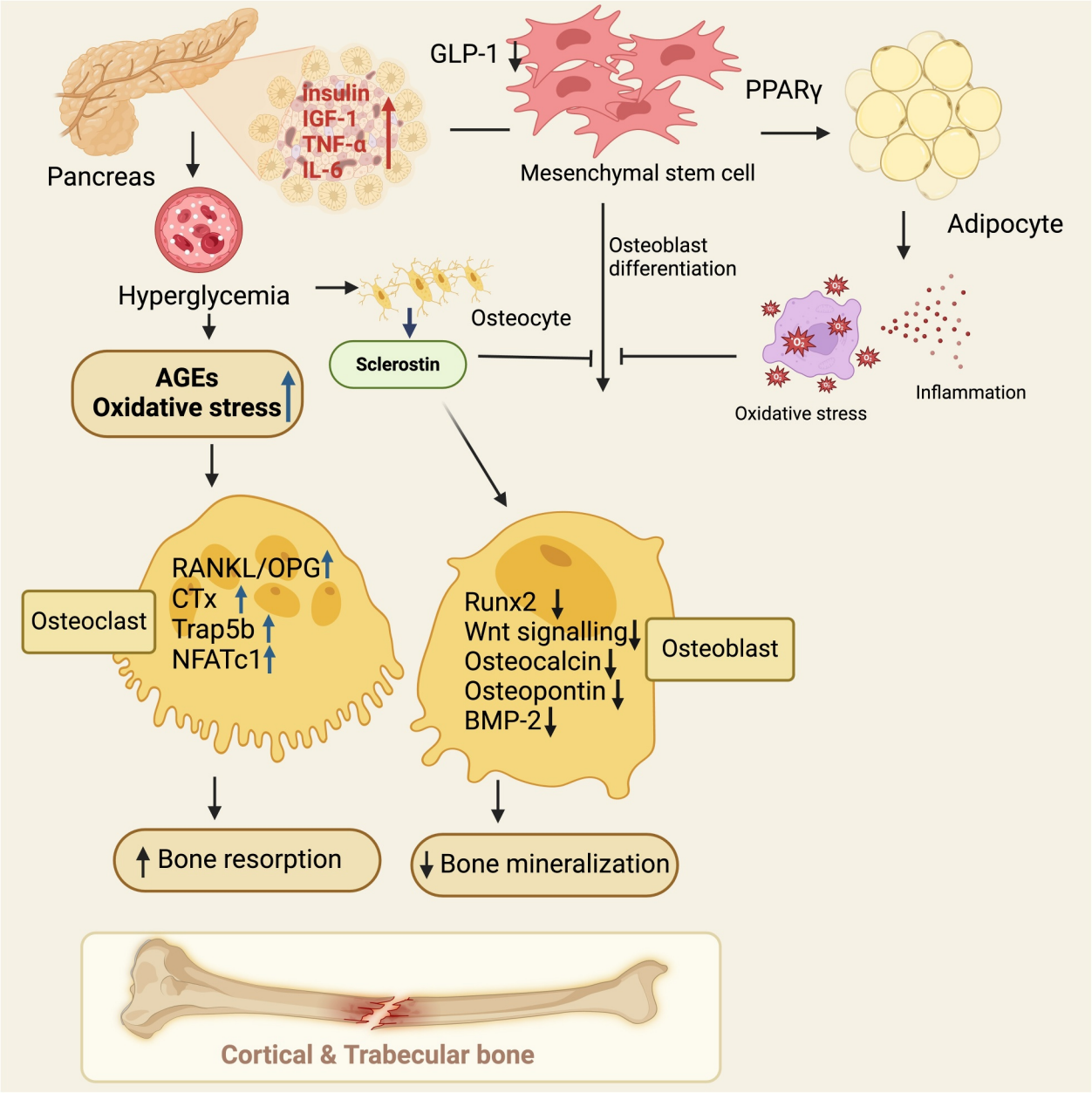

FIGURE 2 | Pathophysiology of diabetes and bone disease (*Created with BioRender.com*). This figure highlights the molecular pathways involved in the pathophysiology of diabetic bone disease. AGEs and oxidative stress: Diabetes elevates advanced glycation end products (AGEs) and oxidative stress, which stimulate osteocytes to produce sclerostin. This inhibits osteoblast differentiation from mesenchymal stem cells, diverting them towards adipocyte formation via the PPARγ (Peroxisome proliferator-activated receptor) pathway, thereby increasing inflammation and oxidative stress. Osteoclast activity: An increase in key osteoclast markers such as RANKL (Receptor activator of nuclear factor-κB ligand)/OPG ratio, CTx, Trap5b (Tartrate-resistant acid phosphatase 5b), and NFATc1 (Nuclear factor of activated T cell) increases bone turnover, leading to high bone resorption. Osteoblast activity: In contrast, osteoblast function is reduced with lower expression of RUNX2, Wnt signalling, osteocalcin, osteopontin, and BMP-2, promoting bone mineralisation.

the mineralisation necessary for healthy bone development [22]. Primarily produced by the liver, IGF-1 is essential for normal bone growth and maintenance. Studies have consistently shown a positive correlation between serum IGF-1 levels and bone mineral density, indicating that lower levels of IGF-1 are linked to weaker bones and a higher likelihood of fractures [23].

Previous studies also highlight the role of insulin and other pancreatic hormones as anabolic factors in bone formation [24]. In one in vitro study, the disruption of the gene encoding the IGF-1 receptor in osteoblasts impaired their proliferation and mineralisation, a defect that was corrected with insulin treatment [25]. Moreover, in vivo studies on murine models suggest that IGF-1 is pivotal for the terminal differentiation of mesenchymal stem cells (MSCs) into osteoblasts [26]. This underscores the direct role that insulin plays in regulating osteoblastic activity through its surface receptors, while IGF-1 enhances the insulin signal through its interaction with IGF-1

receptors. In T1D, absolute insulin deficiency (insulinopenia) combined with low levels of IGF-1 significantly inhibits bone formation by impairing the function of osteoblasts and their progenitor cells, particularly in the early stages of the disease [26]. In T2D, this inhibitory effect, driven by low insulin and IGF-1 levels, becomes more pronounced as the disease advances. Since T1D typically occurs in children, adolescents, and young adults, the absence of insulin during critical periods of skeletal growth can severely impact bone accrual and the attainment of peak bone mass, particularly in cases of poorly controlled T1D [21]. Both insulin and IGF-1 are vital for bone health by influencing the activity and function of osteoblasts. In diabetes, the dysregulation of these hormones significantly impacts bone metabolism, leading to a range of bone-related issues. While early-stage T2D may temporarily benefit bone mineralisation, the long-term outlook for both T1D and advanced T2D patients includes an increased risk of reduced bone density and fractures due to declining insulin and IGF-1 levels. This underscores the importance of managing diabetes effectively to maintain not only metabolic health but also bone health [6].

2.2 | Hyperglycemia and AGEs

Hyperglycemia, a common feature of diabetes, negatively impacts bone health by inhibiting the function of osteoblasts and osteocytes, the cells responsible for bone formation and maintenance. High glucose levels impair extracellular matrix synthesis, slow down mineralisation, and promote osteoblast apoptosis and senescence, leading to reduced bone formation [27]. This deterioration in cellular activity weakens bone structure and increases the risk of fractures. In a hyperglycaemic environment, the osteocyte lacuno-canalicular system —the network that supports bone remodelling—suffers structural disruptions, which contribute to poor bone quality [28]. Moreover, hyperglycemia activates osteoclasts, increasing bone resorption and further impairing bone strength. AGEs also play a critical role in the development of bone fragility in diabetes. AGEs are formed through the non-enzymatic glycation of proteins, such as collagen, in the bone matrix. As AGEs accumulate in bone tissue, they negatively affect collagen elasticity, leading to stiffer and more brittle bones. The abnormal cross-linking of collagen fibres caused by AGEs reduces the mechanical strength of bones, making them more susceptible to fractures [29]. Additionally, AGEs inhibit osteoblast differentiation and reduce alkaline phosphatase expression, key elements in bone formation. This dual impact on collagen structure and osteoblast function accelerates bone fragility in diabetic patients. The presence of AGEs in bone cells also triggers inflammatory responses that further impair bone health. By binding to the receptor for advanced glycation end products (RAGE) on osteoblasts, AGEs stimulate the production of pro-inflammatory cytokines such as TNF-α (Tumour Necrosis Factor- α), IL-1β (Interleukin-1β), and IL-6 (Interleukin-6). These inflammatory signals contribute to osteoblast death and promote osteoclastogenesis, leading to an imbalance between bone formation and resorption [30]. This chronic inflammatory state is particularly harmful in the early stages of T1D, where reduced bone accrual is common. Increased RANKL expression, which promotes osteoclast activity, further exacerbates bone loss in the hyperglycaemic environment [3]. Studies have shown that AGEs also interfere with bone collagen's structural integrity by disrupting the balance between enzymatic and non-enzymatic cross-links. In healthy bone, enzymatic cross-links between collagen fibres enhance bone strength and elasticity, but AGEs replace these beneficial bonds with non-enzymatic cross-links, resulting in a more brittle bone structure [31]. For example, in diabetic WBN/Kob rats, the accumulation of pentosidine, a type of AGE, was associated with a decrease in enzymatic cross-links and impaired bone biomechanics, despite no change in BMD. This suggests that even in cases where BMD remains stable, AGEs can significantly compromise bone quality and increase fracture risk [32]. AGEs not only affect bone cells but also contribute to the overall inflammatory cycle in diabetic bone disease. Their presence increases sclerostin expression, a factor that inhibits bone formation, and decreases RANKL expression, reducing bone resorption. This combination of effects worsens bone fragility over time. However, research indicates that Galectin-3, a protein found in bone tissue, may counteract some of the harmful effects of AGEs by promoting their removal and reducing their interaction with RAGE, offering a potential protective mechanism against diabetes-related bone damage [33].

2.3 | Pro-Inflammatory Cytokines and Oxidative Stress

Diabetes is intrinsically linked with chronic inflammation, which severely impacts bone health by disrupting the intricate balance of bone remodelling. Elevated levels of pro-inflammatory cytokines, such as TNF-α and IL-6, are common in diabetic patients and play a significant role in bone degradation [34]. TNF-α accelerates bone resorption by stimulating the proliferation and differentiation of osteoclast precursors, thereby enhancing osteoclast activity and exacerbating bone breakdown [35]. Concurrently, IL-6 further exacerbates this process by promoting osteoclast differentiation and increasing bone matrix degradation, leading to a weakened bone structure. The impact of chronic inflammation in diabetes extends beyond cytokine activity [36]. Hyperglycemia, a hallmark of diabetes, intensifies the problem by increasing oxidative stress in the body. High blood glucose levels lead to the excessive production of ROS (Reactive oxygen species). Under normal conditions, ROS are involved in cellular signalling and physiological functions, but in the context of hyperglycemia and inflammation, ROS levels become excessively high, causing oxidative damage.

This oxidative stress accelerates the apoptosis of bone marrow MSCs (mesenchymal stem cells), which are essential for bone formation [37]. The loss of these stem cells impairs the body's ability to generate new bone, contributing to the development of diabetic bone disease. In addition to the effects of inflammatory cytokines, the hyperglycaemic environment alters the differentiation pathways of MSCs [13]. Rather than differentiating into bone-forming cells, these stem cells increasingly become adipocytes, or fat cells, within the bone marrow. This shift results in greater fat deposition in the bone marrow, which not only displaces bone-forming cells but also releases free fatty acids

and inflammatory cytokines, further perpetuating inflammation and bone degradation. Increased marrow fat exacerbates local inflammation, leading to decreased BMD and a higher risk of fractures [13].

MSC differentiation is regulated by pathways such as WNT signalling and PPAR-γ pathways. WNT signalling promotes osteogenesis, while PPAR-γ, influenced by ROS, favours adipogenesis. Studies have demonstrated that MSCs exposed to high glucose environments exhibit increased expression of adipogenesis markers (e.g., PPAR-γ, LPL, adiponectin, GLUT4, and SREBP1c) and reduced expression of osteogenic markers. This indicates that hyperglycemia shifts MSC differentiation from bone formation towards fat accumulation [38]. Additionally, recent research using rat bone marrow-derived MSCs (BM-MSCs) found that hyperglycemia activates the Notch2 signalling pathway, which negatively correlates with alkaline phosphatase (ALP) expression and inhibits osteoblastogenesis [13]. Hyperglycemia also increases sclerostin production, which promotes adipogenesis by suppressing WNT signalling in human BM-MSCs.

2.4 | Hematopoietic Stem Cells (HSCs) and Its Diabetes Connection

The sympathetic nervous system plays a crucial role in mobilising hematopoietic stem cells (HSCs) into the bloodstream, and clinical studies have shown that the levels of these cells are inversely correlated with cardiovascular events [39]. In diabetes mellitus, however, there is evidence suggesting that the disease leads to structural changes and autonomic neuropathy in the bone marrow. These alterations affect the levels of CD34+ cells in the blood [40]. Research in p66Shc knockout mice has demonstrated that these changes are linked to the downregulation of the Sirt1 gene, which plays a role in this process [41]. In animal models, an insulin-resistant and hyperglycaemic environment has been shown to induce epigenetic modifications in bone marrow through the activation of JMJD3, a histone H3K27 demethylase. This activation leads to increased expression of inflammatory cytokines. Notably, these epigenetic changes persist in peripheral monocytes, suggesting that the diabetic bone marrow environment may alter macrophage function and contribute to ongoing inflammation [42]. Additionally, inhibition of dipeptidyl peptidase-4 (DPP-4) has been observed to increase the circulation of HSCs in humans, indicating that DPP-4 dysregulation might play a significant role in impaired HSC mobilisation associated with diabetes mellitus [43].

Animal studies have shown a correlation between diabetes and increased bone marrow adiposity, suggesting that changes in marrow fat composition may contribute to diabetic fragility fracture. Research indicates that diabetic models have higher bone marrow fat content and altered fat composition compared with healthy controls. While these findings suggest a link between diabetes and increased marrow adiposity, it remains unclear whether diabetes directly causes this increase or if obesity is a confounding factor [44]. In T2D, insulin resistance further complicates bone health. Insulin-resistant cells are less likely to store lipids, leading to increased fat deposition in the bone marrow, which correlates with altered hormone levels and increased visceral adiposity. White adipose tissue (WAT) in diabetic individuals shows higher levels of inflammation compared with that in obese individuals without diabetes [45]. Hypoxic conditions in hypertrophic adipocytes increase hypoxia-inducible factor 1-alpha (HIF-1α), which triggers inflammatory cytokine expression like TNF-α, contributing to insulin resistance and bone degradation [46]. In vitro models suggest that chronic inflammation in diabetes results from a combination of a hyperglycaemic bone marrow environment and oxidative stress, which inhibits osteoblast maturation and shifts MSC differentiation from osteoblastogenesis to adipogenesis. This creates a vicious cycle of metabolic stress that maintains chronic inflammation, leading to demineralisation of the trabecular bone and increased ROS production. The understanding of T2D as a cycle of chronic inflammation has opened avenues for developing anti-inflammatory treatments. For example, streptozotocin-induced T2D mouse models have shown reduced expression of transcription factors required for MSC osteoblastic differentiation. Similarly, diabetic mice exhibit fewer viable MSCs with functional impairments [47]. Further research into the effects of hyperglycemia, AGEs, and oxidative stress on human MSCs is needed.

3 | Underlying Mechanisms

In diabetes, bone disease arises from underlying mechanisms that compromise bone quality and elevate fracture risk. Diabetes impacts bone health through altered gut hormone regulation, dysbiosis of gut microbiota, and microvascular disease. These changes disrupt bone turnover, affecting both trabecular and cortical bone. These mechanisms include altered bone turnover and changes in bone material properties, leading to weaker bones. Exploring bone quality involves examining both the rate of bone remodelling and the intrinsic properties of bone tissue. Understanding these factors is crucial for assessing fracture risk in diabetic patients, as traditional bone density measurements may not fully capture the increased vulnerability to fractures seen in this population.

3.1 | Bone Turnover

Bone turnover markers provide indirect measures of these effects, revealing key differences between individuals with diabetes and healthy controls. Osteocalcin, a marker of bone formation produced by osteoblasts, is notably decreased in patients with both T1D and T2D, with levels inversely correlated with HbA1c. In particular, children with T1D exhibit low osteocalcin levels, and derivatives of furanocoumarins have been shown to reverse the suppression of osteocalcin and improve trabecular thickness in diabetic mice by down-regulating osteoclast-related genes such as RANKL [48].

In T2D, sclerostin—a marker for bone resorption—has been found to be elevated and negatively correlated with bone formation. Though this link is well-established in T2D, its role in T1D remains unclear. Bone turnover markers such as osteocalcin and sclerostin could serve as valuable tools for predicting

fracture risk in diabetic patients in future studies [49]. Recent research has explored 'signature miRNAs' involved in bone turnover, with findings linking specific miRNAs to diabetic fragility fractures [50]. A 2016 study identified miR-550a-5p, miR-96-5p, miR-382-3p, and miR-181c-5p as markers associated with T2D-induced fragility fractures [51]. Interestingly, miR-382-3p stimulates osteogenesis and inhibits adipogenesis, with lower levels found in T2D patients with fractures. In contrast, miR-550a-5p, which is a potent inhibitor of osteogenesis, was upregulated in diabetic fracture patients, highlighting the potential role of miRNAs in bone health. In T1D, miR-148a and miR-21-5p have been associated with decreased BMD and elevated circulating parathyroid hormone levels [52].

The Impact of diabetes on osteoclast function remains inconclusive, with studies showing mixed results. While some in vitro and animal studies suggest unchanged bone resorption rates, others indicate increased osteoclastic activity in specific conditions such as periodontal disease and osteoporosis [53]. However, some studies have reported inhibited osteoclast function in a diabetic environment. Overall, the evidence suggests that impaired bone formation in diabetes is more likely driven by inhibited osteoblast and progenitor cell activity rather than altered bone resorption [16]. Further research is needed to clarify the impact of diabetes on osteoclast differentiation and function. Bone turnover in patients with diabetes, particularly T1D and T2D, is lower than in non-diabetic individuals. Studies using bone biopsies have shown reduced bone turnover in both T1D and T2D, though some results are limited by small sample sizes [54]. For instance, a study using transiliac biopsies from 18 T1D patients found no significant differences in bone turnover compared with controls. However, these patients had well-regulated glucose levels (mean HbA1c of 6.8%), which may have influenced the results [55]. Meta-analyses have consistently shown lower levels of bone resorption markers like C-terminal cross-linked telopeptide (CTX) and formation markers like procollagen type 1 amino terminal propeptide (P1NP) and osteocalcin in diabetic patients [56]. Interestingly, these studies also revealed higher serum levels of sclerostin in T1D and T2D patients, suggesting that hyperglycemia may trigger osteocyte dysfunction, leading to increased sclerostin levels and impaired bone formation [49]. These findings highlight the complex interplay between diabetes, bone health, and bone turnover markers, emphasising the need for further exploration of these mechanisms.

3.2 | Bone Material Properties

AGEs and bone microarchitecture play critical roles in understanding how diabetes affects bone health. AGEs accumulate in bone through nonenzymatic glycation of collagen, impacting bone material properties [57]. Studies show that AGE levels are significantly higher in patients with T2D than in healthy controls, with AGEs linked to osteoporosis, particularly in postmenopausal women [58]. AGE-modified collagen inhibits osteoblastic function and differentiation, further complicating bone health in diabetic environments. Moreover, AGEs also interfere with osteoclast differentiation, affecting the balance between bone formation and resorption [59].

In both T1D and T2D, BMD is a critical factor in fracture risk, but the effects differ. T1D patients tend to show reduced BMD at the spine, hip, and whole body, although the magnitude of these reductions varies across studies, ranging from 8% to 67%. A 2022 meta-analysis found average BMD decreases of 22% at the spine and 37% at the hip [8]. While the duration of diabetes influences the severity of BMD loss, glycaemic control (HbA1c levels) does not seem to mitigate this decline. Furthermore, poor bone quality, in addition to reduced BMD, contributes to the higher fracture risk in T1D patients. T2D presents a paradox, as patients generally exhibit higher BMD, particularly in the hip, yet have an increased fracture risk. This may be due to diabetes-related complications such as neuropathy, hypoglycemic episodes, and the use of certain antidiabetic medications, which increase the risk of falls. However, even when fall risk is accounted for, T2DM patients continue to exhibit a higher fracture risk, suggesting that impairments in bone quality and architecture play a significant role [60].

High-resolution peripheral quantitative computed tomography (HR-pQCT) has been used to study bone microarchitecture in diabetes, particularly T2D [61]. However, the findings are often conflicting. One study involving 19 patients with T2D showed increased cortical porosity at the radius and tibia compared with healthy controls [62]. Another, larger study of 190 men with T2D found decreased total bone surface area and reduced bone strength in the cortices of the radius and tibia [63]. A third study on postmenopausal women with and without diabetes found that those with T2D and a history of fractures exhibited greater cortical porosity than those without fractures, while no such differences were observed in the non-diabetic control group [64]. A more recent study of over 1000 participants revealed that T2D was associated with decreases in cortical bone density and tibial bone surface area, as well as increased cortical porosity, though these changes were moderate [65]. Notably, the trabecular parameters in patients with T2D were better than in those without diabetes. Patients with T2D and fractures had lower tibial volumetric BMD and radial cortical thickness, further indicating the role of bone architecture in fracture risk [66]. In some studies, HR-pQCT parameters showed no significant differences between T2D patients and controls, underscoring the variability in study outcomes [61]. For instance, a small study of 25 individuals found no differences in bone microarchitecture or strength parameters. The trabecular bone score (TBS), which measures bone texture and quality, has also been investigated in T2D patients [67]. Although BMD values in T2D patients tend to be elevated, TBS values are often lower, indicating potential microarchitectural deficits that contribute to increased fracture risk. The bone health of T1D patients is further compromised by the failure of pancreatic beta cells and low levels of IGF1. This deficiency inhibits the differentiation of mesenchymal stem cells into osteoblasts and suppresses osteoblastic activity, leading to reduced skeletal growth and insufficient peak bone mass during youth [68]. Conversely, T2D impacts bone health later in life, where factors such as insulin deficiency, hyperglycemia, chronic inflammation, AGE accumulation, and microvascular disease degrade bone architecture and biomechanical properties. These effects collectively increase the relative risk of fractures, particularly at the hip, as T2D progresses. Recent imaging studies, including those utilising in vivo micro-indentation, have confirmed structural changes in diabetic bone [69]. T2D

patients showed significantly higher cortical porosity and lower bone mineral strength compared with healthy controls, highlighting the importance of evaluating bone architecture and not just BMD when assessing fracture risk in diabetic patients. Increased bone marrow adiposity, often associated with obesity, has also been observed in diabetes, but its specific contribution to bone quality remains unclear [44]. In addition to neuropathy, hypoglycemic episodes, and antidiabetic medications, chronic liver diseases are directly related to bone fracture risk. Majorly bone loss is impared by vitamin D activation, reducing calcium absorption, and triggering bone demineralisation. Hormonal imbalances, such as hypogonadism, decrease bone formation, while chronic inflammation and malnutrition worsen bone health. Low calcium levels stimulate parathyroid hormone, increasing bone resorption. Alcoholic liver disease and medications, such as glucocorticoids, further contribute to osteoporosis and fractures. These mechanisms lead to conditions like osteoporosis and osteomalacia, which require management through adequate nutrition, vitamin D and calcium supplementation, and treating the underlying liver disease [70].

These studies collectively emphasise that diabetes alters bone material properties through mechanisms such as AGE accumulation, hyperglycemia, and inflammation. These alterations weaken the bone, making diabetic patients more susceptible to fractures, even when traditional bone density measurements suggest otherwise. Understanding these mechanisms is crucial for developing better strategies to prevent and manage fractures in diabetic patients.

3.3 | Gut Hormone

The gastrointestinal tract (GIT) plays a crucial role in regulating various physiological processes, including hormone secretion, metabolism, and bone health. Recently, there has been growing interest in GIT-derived peptide hormones, particularly in relation to their roles in bone integrity and the pathophysiology of obesity and diabetes [71]. The incretin hormones, glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1), are among the most studied peptides in this context, as they have been implicated in both metabolic and skeletal functions [72].

GLP-1 and GIP are incretin hormones that are secreted in response to food intake and stimulate insulin release, which helps regulate blood sugar levels. Generally, diabetes is associated with a lower level of GLP-1 [73]. GLP-1 mimetics are now widely used for treating obesity and T2D. Furthermore, tirzepatide, a dual GLP-1/GIP receptor agonist, has been recently approved for clinical use in managing both conditions. The link between these incretin hormones and bone health is an area of increasing interest, particularly because their secretion and activity are altered in obesity and diabetes, which may negatively affect bone quality. Beyond GLP-1 and GIP, another closely related hormone, glucagon-like peptide-2 (GLP-2), has garnered attention for its significant effects on bone metabolism [74].

GLP-2, a 33-amino-acid peptide encoded by the proglucagon gene, was initially recognized for its ability to promote intestinal growth. Like GLP-1, GLP-2 is rapidly degraded by the enzyme dipeptidyl peptidase-4 (DPP-4), limiting its therapeutic potential. However, the development of DPP-4-resistant forms, such as teduglutide, has allowed GLP-2 to be used clinically for treating short bowel syndrome. Beyond its intestinal effects, GLP-2 has been shown to enhance BMD, improve calcium absorption, and reduce bone resorption in both animals and humans [72]. Clinical studies in postmenopausal women, a population at high risk for osteoporosis, have confirmed GLP-2's capacity to suppress bone turnover and promote bone growth [75]. Interestingly, GLP-2 receptors have been found on osteoclast cells, indicating a direct role for GLP-2 in bone resorption processes. GLP-2 may also exert effects via the gut-pancreas-bone axis, a system that could involve interactions with parathyroid hormone (PTH), a key regulator of bone remodelling [76].

While GLP-2's effects on bone are well-documented, its role in osteoblast (bone-forming cell) activity remains unclear. GLP-2 receptors have only been definitively identified in osteoclasts, suggesting that GLP-2's bone benefits may be mediated through indirect pathways involving PTH. Interestingly, studies suggest that gut function, especially in the jejunum, might be essential for GLP-2's bone-protective effects via PTH signalling (Figure 3) [77].

The incretin hormones GIP and GLP-1 are also known to influence bone metabolism. Both hormones promote glucose-stimulated insulin secretion and have been shown to impact bone health. GLP-1, for instance, has been found to stimulate osteoblast proliferation and differentiation while inhibiting osteoclast activity, thus preventing bone loss and maintaining bone quality. In mouse models, GLP-1 receptor knockout leads to a decrease in cortical bone thickness, indicating its vital role in maintaining bone structure. Moreover, GLP-1 receptor activation has been linked to improved fracture healing in animal models. Despite these findings, the presence of functional GLP-1 receptors in bone remains a subject of debate, suggesting that its skeletal effects may be indirect and related to its insulinotropic actions [72].

GIP, on the other hand, exerts more direct effects on bone. GIP receptors are present on both osteoblasts and osteoclasts, and studies have shown that GIP enhances osteoblast survival and reduces osteoclast activity. In rodents, GIP promotes bone formation, and GIP receptor knockout leads to compromised bone strength and quality. The signalling pathways involved in GIP's effects on bone include the cAMP/PKA pathway, the MAPK/ERK pathway, and the PI3K/Akt pathway, all of which play crucial roles in bone matrix synthesis and mineralisation. Notably, GIP's bone-protective effects have been observed in both healthy individuals and those with T1D, highlighting its therapeutic potential for various populations [78].

One of the challenges in harnessing the therapeutic potential of incretin hormones for bone health is their short half-life, which limits their clinical utility. To address this, long-acting analogues of GIP and GLP-1 have been developed. These analogues have been extensively studied for their roles in treating obesity and diabetes [79]. For instance, exendin-4, the first GLP-1 mimetic approved for T2D treatment, has been shown to improve bone strength and prevent trabecular bone deterioration in animal models of bone loss [80]. Similarly, liraglutide, a

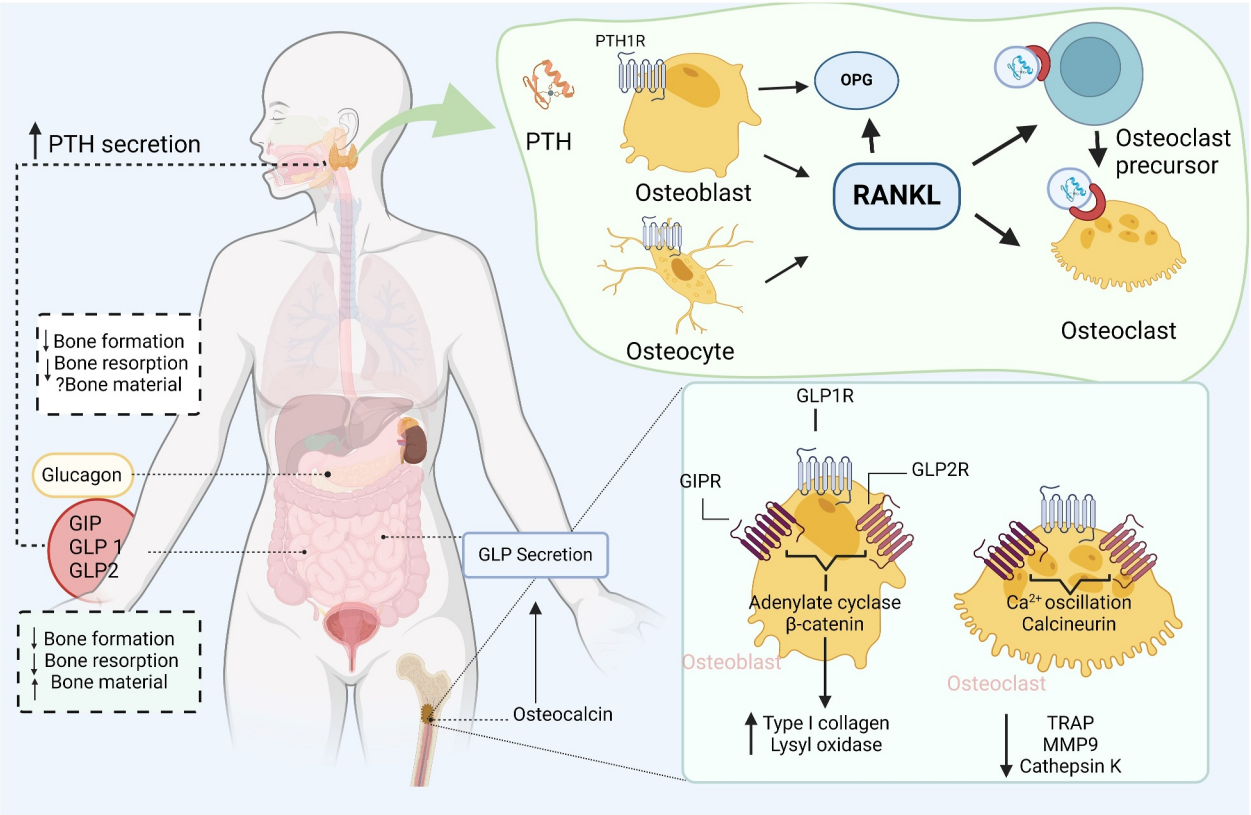

FIGURE 3 | Schematic representation of gut hormone-bone tissue cross-talk (*Created with BioRender.com*). This figure illustrates the roles of GIP, GLP-1, GLP-2, and glucagon in bone formation, bone resorption, and material regulation. These hormones interact with their respective receptors (GIPR, GLP-1R, and GLP-2R) on osteoblasts and osteoclasts, modulating the adenylate cyclase and oscillation calcineurin pathways. This modulation leads to the upregulation of type I collagen and lysyl oxidase in osteoblasts and the downregulation of TRAP, MMP9, and cathepsin K. Additionally, GIP, GLP-1, and GLP-2 influence PTH secretion, which interacts with PTH1R on osteoblasts and osteocytes, affecting RANKL expression and osteoclast precursor modulation. GIP, glucose-dependent insulinotropic polypeptide; GIPR, glucose-dependent insulinotropic polypeptide receptor; GLP, glucagon-like peptide; GLP1R, glucagon-like peptide-1 receptor; GLP2R, glucagon-like peptide-2 receptor; MMP9, matrix metallopeptidase 9; OPG, osteoprotegerin; PTH, parathyroid hormone; PTHR, parathyroid hormone receptor; RANKL, receptor activator of nuclear factor kappa-B ligand; TRAP, tartrate-resistant acid phosphatase.

long-acting GLP-1 analogue, has been found to reduce osteoclast numbers, increase osteocalcin levels, and prevent bone mineral loss in diabetic animals [81].

In humans, long-acting GLP-1 receptor agonists have been shown to increase bone formation and improve BMD in individuals with obesity and T2D [5]. Similar findings have been reported with long-acting GIP analogues, such as (D-Ala2) GIP, which improves bone quality and fracture resistance in diabetic mice [82]. These analogues offer a promising approach for treating the 'bone fragility diabetes paradox', a phenomenon in which individuals with T2D have normal BMD but increased fracture risk due to compromised bone quality. The development of dual and triple receptor agonists, such as tirzepatide, represents an exciting new frontier in bone-targeted therapies. Tirzepatide has a greater affinity for GIP than GLP-1 receptors and offers combined benefits for bone health by acting on both pathways. Other dual- and triple-acting peptides that target GIP, GLP-1, and glucagon receptors are also being developed and have shown promising results in animal studies, further supporting the potential of these compounds for treating bone disorders in obesity and diabetes [83].

Beyond incretins, other GIT-derived peptides may also impact bone health. For example, DPP-4 inhibitors, which prevent the degradation of GIP, GLP-1, and GLP-2, have been shown to improve BMD and bone quality in animal models of diabetes. These findings suggest that DPP-4 inhibitors, which are already approved for T2D treatment, may offer additional benefits for bone health [84, 85].

Peptide hormones such as PTH, calcitonin, ghrelin, and leptin also play roles in bone metabolism. PTH is a well-known osteoporotic medication, and its bone-forming effects have been observed in diabetic animal models. Calcitonin, which opposes PTH action, promotes bone formation by upregulating osteogenic pathways. Ghrelin and leptin, both produced by adipocytes and pancreatic islets, have been shown to enhance osteoblast activity and may influence bone turnover through their actions on the gut-bone axis [16].

GIT-derived hormones, particularly the incretin peptides GIP, GLP-1, and GLP-2, play critical roles in bone metabolism. These hormones and their analogues offer promising therapeutic opportunities for treating bone disorders in the context of obesity

and diabetes. However, further research is needed to fully understand their mechanisms of action and to translate these findings into effective clinical treatments (Figure 3).

3.4 | Gut Microbiota

The gut microbiota plays a crucial role in the regulation of metabolic and skeletal health, particularly in diabetes, through various mechanisms involving bacterial species and their metabolites, such as short-chain fatty acids (SCFAs). Emerging evidence suggests that gut dysbiosis, characterised by an imbalance in microbial composition, is a key contributor to the development of both diabetes and bone disorders. In individuals with diabetes, alterations in the gut microbiota have been linked to increased gut permeability, systemic inflammation, and insulin resistance, all of which have downstream effects on bone health [77]. Certain bacterial species, including *Akkermansia muciniphila*, *Bacteroides fragilis*, *Bifidobacterium longum*, and *Lactobacillus rhamnosus*, have been shown to have beneficial effects on metabolic and bone health through their production of SCFAs, such as butyrate, acetate, and propionate, which modulate host physiology by interacting with G protein-coupled receptors (GPCRs) and inhibiting histone deacetylases (HDACs). SCFAs serve as a critical link between the gut microbiota, metabolism, and bone, as they regulate glucose homoeostasis and inflammatory pathways, both of which impact bone remodelling [86].

Experimental studies demonstrate that butyrate, produced by bacteria like *Roseburia* and *Faecalibacterium prausnitzii*, enhances insulin sensitivity by stimulating GLP-1 secretion and activating AMPK in skeletal muscle, improving glucose uptake. This regulation of glucose metabolism is vital in diabetes management and indirectly influences bone health by reducing hyperglycemia-induced oxidative stress and inflammation, which can impair bone formation. In particular, SCFAs have been shown to enhance osteoblast differentiation and mineralisation while simultaneously inhibiting osteoclastogenesis. Butyrate, for example, promotes the differentiation of mesenchymal stem cells into osteoblasts through the activation of the Wnt/β-catenin signalling pathway, essential for bone formation. Additionally, butyrate inhibits NF-κB signalling, which reduces pro-inflammatory cytokines like TNF-α and IL-6 that are known to drive osteoclast-mediated bone resorption. The inhibition of osteoclast activity by SCFAs helps preserve BMD, which is often compromised in diabetic patients due to systemic inflammation and insulin resistance [87].

Clinical studies provide further evidence supporting the role of gut microbiota in modulating bone health in diabetes. For instance, diabetic patients with low BMD exhibit a different gut microbial profile compared to healthy individuals, with reduced levels of SCFA-producing bacteria such as *Bifidobacterium* and *Faecalibacterium*, coupled with increased abundance of pro-inflammatory species like *Escherichia coli*. The altered gut microbiota composition is associated with lower SCFA production, which weakens the gut-bone axis. SCFAs are known to enhance calcium absorption in the intestines by regulating the expression of calcium-binding proteins, such as calbindin-D9k, and promoting the intestinal uptake of calcium via GPR41/43 signalling. This mechanism is crucial in maintaining adequate calcium levels for bone mineralisation, particularly in diabetic patients who are at risk of reduced calcium absorption due to gut dysbiosis [88].

Furthermore, experimental studies involving germ-free mice have demonstrated that the absence of gut microbiota results in decreased bone mass and impaired glucose metabolism, reinforcing the integral role of microbial communities in maintaining bone and metabolic health. When germ-free mice were colonised with SCFA-producing bacteria, there was a notable improvement in both insulin sensitivity and bone quality [89]. Butyrate supplementation in diabetic mouse models has also been shown to restore bone mass by increasing the number of osteoblasts and reducing osteoclast activity, as well as decreasing markers of systemic inflammation, such as C-reactive protein (CRP) and IL-1β. In humans, probiotic interventions with strains like *Lactobacillus reuteri* and *Bifidobacterium lactis* have been observed to enhance SCFA production, leading to improved markers of bone health and reduced insulin resistance in diabetic patients [90].

In addition to SCFAs, other bacterial metabolites like indole-3-propionic acid (IPA), produced by *Clostridium sporogenes*, have been shown to exert protective effects on both bone and metabolic health. IPA is an antioxidant that modulates bone resorption by inhibiting osteoclast differentiation through downregulation of RANKL and upregulation of osteoprotegerin (OPG), contributing to reduced bone loss in diabetes. The presence of IPA in the gut also enhances intestinal barrier function, preventing the translocation of endotoxins like LPS into the bloodstream, which can trigger systemic inflammation and exacerbate bone degradation [91].

The interplay between gut microbiota and the immune system further highlights the mechanisms through which bacteria influence bone health in diabetes. SCFAs and microbial metabolites modulate the differentiation of regulatory T cells (Tregs) and macrophages, both of which are involved in bone remodelling. In particular, butyrate has been shown to promote the expansion of Tregs, which suppress osteoclastogenesis by inhibiting the production of pro-inflammatory cytokines and favouring the secretion of anti-inflammatory cytokines such as IL-10. This immune-mediated mechanism helps reduce the inflammatory environment that is prevalent in diabetic patients, thereby protecting against bone loss [92].

Clinical and experimental studies consistently demonstrate that restoring a healthy gut microbiota through probiotic interventions, SCFA supplementation, or dietary modifications can positively impact both glucose metabolism and bone health in diabetic patients. The gut-bone axis represents a promising target for therapeutic interventions aimed at preventing or mitigating the skeletal complications associated with diabetes (Figure 4).

3.5 | Microvascular Issues

Chronic hyperglycemia, regardless of diabetes type, significantly raises the risk of microvascular complications, including

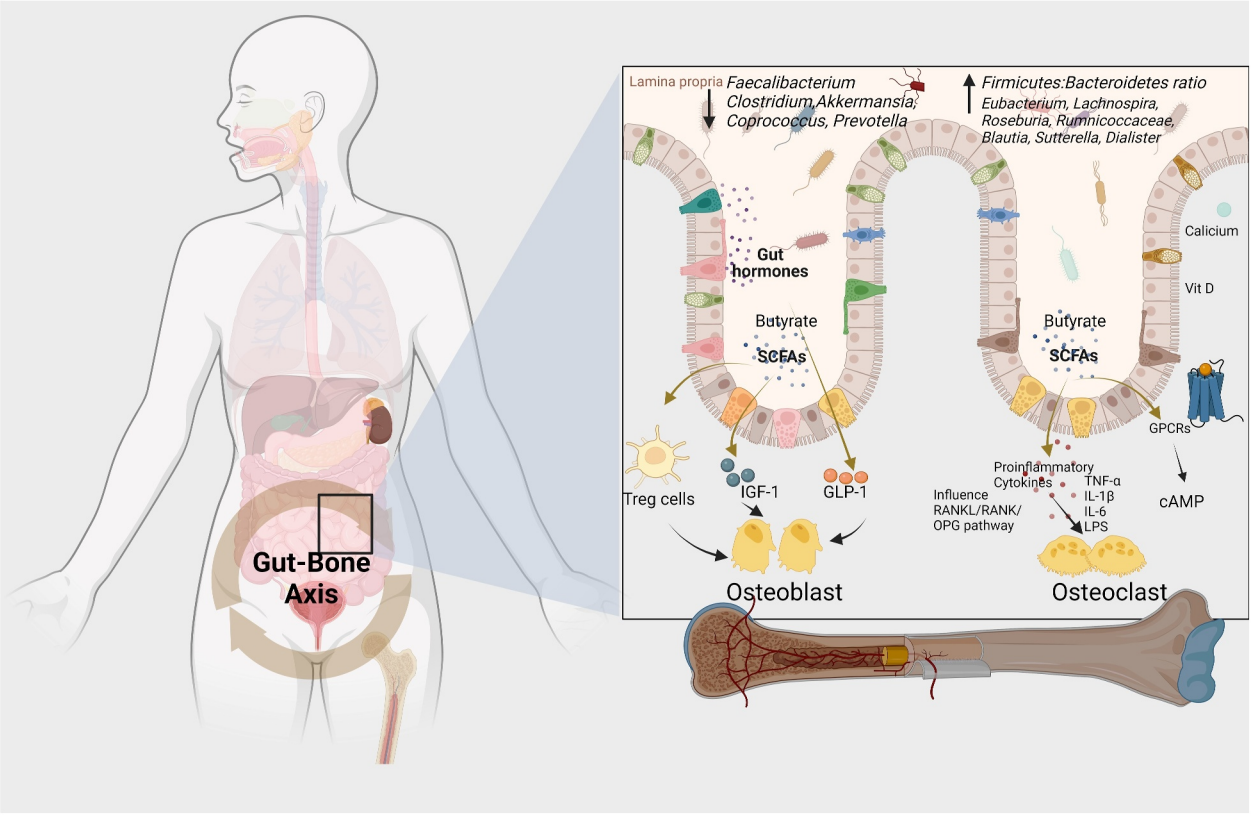

FIGURE 4 | Schematic diagram of SCFAs participating in bone metabolism regulation via multiple approaches (*Created with BioRender.com*). This figure depicts how changes in the abundance of various bacteria, including *Faecalibacterium*, *Clostridium*, *Akkermansia*, *Coprococcus*, and *Prevotella*, as well as the increased *Firmicutes*: *Bacteroidetes* ratio, *Eubacterium*, *Lachnospira*, *Roseburia*, *Ruminococcaceae*, *Blautia*, *Sutterella*, and *Dialister*, lead to elevated levels of butyrate, a SCFAs. Butyrate modulates IGF-1, GLP-1, and Treg levels, impacting osteoblast activity and bone health. Additionally, butyrate reduces pro-inflammatory cytokines, influences the RANKL/OPG pathway and GPCRs for cAMP, and increases calcium levels, thereby maintaining vitamin D levels over the osteoclast activity to maintain bone health. Ca, calcium; cAMP, cyclic adenosine monophosphate; GLP-1, glucagon-like peptide-1; GPCRs, G-protein-coupled receptors; IGF-1, insulin-like growth factor-1; IL-1β, interleukin-1β; IL-6, interleukin-6; LPS, lipopolysaccharide; OPG, osteoprotegerin; RANK, receptor activator of nuclear factor-kB; RANKL, receptor activator of nuclear factor-kB ligand; SCFAs, short chain fatty acids; Th 17, T helper cell 17; TNF-α, tumor necrosis factor-α; Tregs, regulatory cells; Vit D, vitamin D.

retinopathy, neuropathy, and nephropathy, as well as macrovascular disease. The severity and duration of hyperglycemia correlate with an increased risk, which can begin shortly after diagnosis. Even prediabetes is linked to a higher risk of microvascular disease. No glucose level guarantees zero risk, and glycaemic variability, characterised by frequent glucose fluctuations, is an emerging risk factor that exacerbates complications through oxidative stress. These vascular complications contribute to the premature morbidity and mortality in diabetes and account for much of the healthcare burden. Extrinsic factors, such as obesity-induced mechanical loading or glucose-lowering drugs, particularly insulin and thiazolidinediones, also influence the pathogenesis of diabetic osteopathy in T2D (Figure 1) [93].

The role of microvascular complications in diabetic bone disease has become a subject of increasing research interest, although its contribution remains debated. Microangiopathy in diabetes has been linked to arteriole, capillary, and sinusoid rarefaction in the bone marrow, accompanied by basement membrane thickening and fat accumulation. These changes are compounded by pericyte dysfunction, reduced perfusion, impaired responsiveness to pro-angiogenic signals, and a shortage of regenerative macrophages, which collectively hinder bone regeneration and repair. Meta-analyses have revealed imbalances in bone turnover biomarkers, such as elevated serum levels of procollagen type 1 N-terminal propeptide (P1NP), parathyroid hormone, C-terminal telopeptide (CTX), and osteocalcin, alongside reduced levels of 25-hydroxyvitamin D3 (25(OH)D3), indicating impaired bone metabolism in diabetic patients with microvascular complications. These findings suggest that diabetic microangiopathy is closely linked to compromised bone health, increased risk of bone loss, osteoporosis, and impaired fracture healing [94].

Endothelial dysfunction is a key feature of diabetic microangiopathy, where the nitric oxide (NO) pathway is particularly affected. Hyperglycemia decreases endothelial NO synthase (eNOS) activity, leading to reduced NO bioavailability, which is critical for vasodilation and proper blood flow. The impaired NO signalling not only limits blood flow to bone but also affects osteoblastic function as NO plays a role in promoting osteoblast differentiation and activity. Furthermore, diabetic microvascular complications lead to increased production of endothelin-1, a vasoconstrictor, which further exacerbates the reduction in blood supply to bone tissues. This vasoconstriction, coupled

with capillary rarefaction observed in diabetic patients, reduces the overall vascular density within bones, contributing to impaired bone remodelling and regeneration [3].

Clinical studies have demonstrated that diabetic patients exhibit lower bone blood flow and vascular density, particularly in areas like the femoral head, which is highly vascularized and prone to osteonecrosis in diabetes [95]. Experimental models of diabetes also support this observation, showing a clear association between hyperglycemia, reduced bone vascularization, and impaired bone quality. In diabetic rodents, decreased expression of angiogenic factors such as vascular endothelial growth factor (VEGF) has been observed, which further contributes to the diminished vascularization of bone. VEGF is essential for the formation of new blood vessels, and its downregulation in diabetes inhibits angiogenesis, leading to poor bone healing and reduced osteogenesis. The reduced vascular network also limits the recruitment of osteoprogenitor cells to sites of bone formation, impairing the bone repair process [94].

Clinical evidence consistently shows that diabetic patients, particularly those with T1D, are at a higher risk of fragility fractures compared with the general population. Meta-analyses indicate that both T1D and T2D are associated with more than double the risk of fractures, with T1D patients experiencing an even greater excess risk. Despite lower BMD in T1D, this increased fracture risk is attributed to intrinsic bone fragility. In contrast, in T2D, higher fracture risk is paradoxically observed in the presence of normal or elevated BMD, likely due to impaired bone mechanical properties and extrinsic factors such as obesity or the adverse effects of glucose-lowering drugs. Furthermore, a correlation between elevated HbA1c levels and increased fracture risk has been identified, with each 1% increase in HbA1c associated with an 8% higher fracture risk. The use of insulin in T2D patients, particularly its association with hypoglycemia-induced falls, may also contribute to the increased fracture risk [96].

Fracture healing is another significant concern in diabetic bone disease, as diabetic patients face a four-fold increased risk of complications such as non-union, delayed union, and malunion. This impaired healing process is closely tied to the lack of a functional vascular network at the fracture site, which is essential for delivering oxygen and nutrients required for bone repair [8]. Additionally, diabetic patients with microvascular complications, particularly those with retinopathy or nephropathy, exhibit lower BMD and a higher propensity for osteopenia and fragility fractures, as evidenced by longitudinal studies. For instance, prospective studies have shown that patients with T1D who develop microvascular complications experience a more rapid decline in bone mass compared with those without such complications [93].

The impact of microvascular complications on bone microstructure and quality has been demonstrated in both T1D and T2D patients. High-resolution peripheral quantitative computed tomography (HR-pQCT) studies have revealed that T1D patients with microvascular disease exhibit reduced trabecular thickness and bone volume, along with cortical thinning and porosity, compared with patients without diabetes. These structural deficits persist even after adjusting for factors such as diabetes duration and hyperglycemia. Furthermore, bone histomorphometry studies in T1D patients without microvascular complications suggest that bone quality may be preserved in the absence of vascular issues, highlighting the importance of microangiopathy in the progression of diabetic bone disease [97].

In T2D, the relationship between microvascular disease and bone health appears to be mediated by changes in cortical bone architecture, with increased cortical porosity and reduced volumetric BMD observed in patients with a history of fragility fractures. These changes likely contribute to the heightened fracture risk observed in T2D, despite normal or elevated BMD. Limited histomorphometric evidence suggests that chronic complications such as retinopathy and nephropathy in T2D are associated with reduced bone quality, as indicated by thinner osteoid layers and diminished bone formation rates [61].

Fall risk also plays a significant role in fracture incidence among diabetic patients with microvascular complications. Neuropathy and retinopathy, common complications of both T1D and T2D, contribute to impaired balance, poor vision, and postural instability, all of which increase the likelihood of falls. Studies have shown that T1D patients, particularly those with retinopathy or neuropathy, are at higher risk of falls, which in turn raises the risk of fracture. Similarly, T2D patients with microvascular disease are more prone to falls, further compounding their risk of fragility fractures. Despite the well-documented association between microvascular complications and increased fracture risk, it remains unclear whether these complications directly affect bone health or merely serve as markers of more severe diabetes [98].

Microvascular complications play a significant role in impairing bone quality, reducing bone turnover, and increasing the risk of fractures in diabetic patients, particularly those with T1D. Although patients with T2D typically exhibit higher BMD, they remain at an elevated risk of fractures due to impaired bone microstructure and mechanical properties. Further research is required to fully elucidate the intricate mechanisms linking diabetes, microvascular complications, and bone health, as well as to develop targeted therapies to mitigate the risk of fragility fractures in this vulnerable population.

3.6 | Impact of Different Bone Types

Bone is a complex tissue composed of different types that play distinct roles in maintaining skeletal integrity. In the context of diabetic bone disease, both cortical and trabecular bone types are significantly affected, with implications for bone strength and fracture risk.

3.6.1 | Cortical and Trabecular Bone

Cortical bone is responsible for much of the bone's mechanical strength, and its integrity is crucial for load-bearing functions. In both T1D and T2D, cortical bone exhibits increased porosity and thinning, which compromise its mechanical properties and increase the risk of fractures.

In T1D, the lack of insulin directly affects osteoblast activity and bone formation, leading to reduced cortical thickness and increased cortical porosity. These changes are exacerbated by microvascular complications, such as diabetic nephropathy and retinopathy, which further impair bone quality. A study using HR-pQCT to assess bone microarchitecture in T1D patients with and without microvascular complications found that those with complications had significantly reduced cortical thickness and increased porosity compared with those without complications. The impaired bone microarchitecture in T1D patients with microvascular disease is thought to be due to chronic inflammation, oxidative stress, and decreased blood flow to the bone, which impair bone remodelling and regeneration [97].

In T2D, cortical bone quality is similarly compromised, although the mechanisms differ. Insulin resistance and hyperinsulinemia contribute to increased bone turnover, particularly in cortical bone, leading to cortical thinning and increased porosity. Additionally, the toxic effects of AGEs on collagen within the cortical bone matrix reduce bone strength and elasticity. A cross-sectional study using HR-pQCT in T2D patients found that those with a history of fragility fractures had significantly increased cortical porosity compared with non-diabetic controls. This increased porosity, along with decreased cortical thickness, contributes to the higher fracture risk observed in T2D patients, particularly at sites such as the hip and femoral neck, which rely heavily on cortical bone strength [61].

Previous studies on diabetes have provided further insights into the effects of hyperglycemia on cortical bone. In diabetic animal models, chronic hyperglycemia has been shown to impair osteocyte function, leading to reduced bone matrix production and increased bone resorption. Osteocytes, the most abundant cells in cortical bone, play a crucial role in maintaining bone homoeostasis by regulating bone remodelling in response to mechanical stress [99]. In diabetes, the altered function of osteocytes contributes to cortical bone loss and increased fragility. Moreover, diabetic animals exhibit delayed fracture healing and impaired callus formation, which are likely due to the combined effects of insulin deficiency, hyperglycemia, and microvascular complications on bone metabolism.

In clinical studies, patients with T1D have consistently demonstrated lower BMD, particularly in regions rich in trabecular bone, such as the lumbar spine and femoral neck. This reduction in BMD is often accompanied by impaired bone microarchitecture, characterised by decreased trabecular number and thickness. High-resolution peripheral quantitative computed tomography (HR-pQCT) studies in T1D patients have revealed a significant reduction in trabecular bone volume and connectivity, which correlates with an increased risk of fragility fractures, even in the absence of severe trauma. Furthermore, animal models of T1D have shown increased bone marrow adiposity, which may further disrupt the bone remodelling process by inhibiting osteogenesis and promoting adipogenesis within the bone marrow niche [97].

In T2D, the relationship between trabecular bone and diabetes is more nuanced. While BMD is often normal or even elevated in T2D patients, trabecular bone quality is compromised due to factors such as insulin resistance, hyperinsulinemia, and the toxic effects of AGEs on collagen cross-linking within the bone matrix [48]. The accumulation of AGEs in the trabecular bone of T2D patients disrupts collagen integrity, leading to increased bone brittleness and reduced mechanical strength. This paradox of increased BMD but decreased bone quality is commonly referred to as the 'diabetic bone paradox', where patients with T2D exhibit a higher fracture risk despite normal or elevated BMD [67]. Clinical evidence supports this phenomenon, with studies showing that T2D patients have a higher incidence of fractures, particularly at sites rich in trabecular bone, such as the hip, vertebrae, and distal radius [97].

4 | Conclusion

In this review, we attempted to compile an in-depth understanding of diabetic bone disease and the associated fracture risk, shedding light on the multifaceted nature of bone metabolism in diabetic patients. The interplay between metabolic dysregulation, hormonal imbalances, and vascular complications underlies the mechanisms driving bone fragility in diabetes, which affects both trabecular and cortical bone differently depending on the type of diabetes and its specific complications. A key aspect of bone metabolism in diabetes is the role of IGF-1, a hormone critical for bone formation and remodelling. In both T1D and T2D, IGF-1 deficiency, driven by insulin resistance or insulin deficiency, leads to reduced bone turnover, impairing the body's ability to maintain healthy bone structure. Advances in understanding the underlying mechanisms, particularly the roles of IGF-1, AGEs, and the gut-bone axis, provide valuable insights into potential therapeutic strategies aimed at reducing fracture risk and improving bone health in diabetic patients.

5 | Future Perspective

The future of managing diabetic bone disease lies in developing more targeted and comprehensive approaches to address the distinct mechanisms of bone loss in both type 1 and type 2 diabetes. Current fracture risk assessment tools, which often rely on BMD measurements, may be inadequate for diabetic patients, particularly those with type 2 diabetes who present with higher BMD but reduced bone quality. Future research should focus on refining diagnostic tools to incorporate bone quality metrics, advanced imaging techniques, and biomarkers, allowing for more accurate fracture risk prediction in this population. Additionally, investigating the molecular pathways involved in hyperglycemia, AGEs, and gut microbiota may offer new therapeutic targets. Exploring how these factors influence bone metabolism could lead to innovative treatment strategies that specifically address the unique challenges of diabetic bone disease. Personalised medicine approaches tailored to an individual's type of diabetes, bone health status, and metabolic profile will likely play a crucial role in future care. Incorporating skeletal health into standard diabetes management protocols will be essential for reducing fractures and improving the quality of life of patients. Continued research and clinical trials will be necessary to develop effective therapies and preventive strategies for this growing population at risk.

Author Contributions

Prabhat Upadhyay: writing – original draft and figure drawing, conceptualisation. **Sudhir Kumar:** validation, figure drawing and writing – review and editing.

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Ethics Statement

The authors have nothing to report.

Consent

All participants properly consented.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The authors have nothing to report.

Peer Review

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