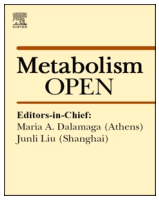
Metabolism Open 24 (2024) 100330

Contents lists available at ScienceDirect

Metabolism Open

journal homepage: www.sciencedirect.com/journal/metabolism-open



Understanding the impact of diabetes on bone health: A clinical review

Preeti Sharma [a,*], Rahul Kumar Sharma [b], Khushboo Gaur [a]

[a] Department of Pharmacy, PSIT-Pranveer Singh Institute of Technology (Pharmacy), Bhauti, Kanpur, 209305, Uttar Pradesh, India
[b] Aryakul College of Pharmacy & Research Sitapur, Village- Jajjaur, Post- Manawa, (Near Krishi Vigyan Kendra Sitapur) Sidhauli, Dist- Sitapur- 261303 U.P, India

ARTICLE INFO

Keywords:
GLP-1
Bone mineral density
Diabetic osteopathy
Gut bone axis

ABSTRACT

Diabetic bone disease, a form of secondary osteoporosis, is characterized by weakened bones and an increased risk of fractures, especially in patients with type 2 diabetes (T2D). This review explores the key mechanisms driving this condition, including hyperglycemia, insulin resistance, advanced glycation end products (AGEs), and proinflammatory cytokines, all of which disturb normal bone turnover by disrupting the functions of osteoblasts and osteoclasts. We examine the roles of bone turnover and mineralization, as well as how microvascular complications affect bone microarchitecture. Additionally, the influence of gut hormones, such as GLP-1 and GIP, and gut microbiota, particularly species like *Akkermansia muciniphila*, on the gut-bone axis is discussed, as these factors play a role in regulating bone density and structure. While T2D patients may show normal or even elevated bone mineral density (BMD), the underlying quality of bone is often compromised, leading to increased fragility. This review integrates current knowledge on the molecular, hormonal, and microbial interactions contributing to diabetic bone disease. By highlighting these pathways, we aim to offer insights into potential therapeutic strategies and inform future research aimed at improving the diagnosis, treatment, and overall management of this condition.

1. Introduction

As the global population continues to age, coupled with shifts in lifestyle and dietary habits, diabetes mellitus (DM) has emerged as a leading public health concern. It now ranks as the third most significant non-communicable disease, surpassed only by cardiovascular diseases and cancer. DM encompasses a spectrum of metabolic disorders, all of which are typified by chronic hyperglycemia stemming from a variety of causes. The most prominent contributors include inadequate insulin production and resistance to insulin's effects [1]. These conditions result in prolonged high blood sugar levels that, if left unchecked, can cause widespread damage to several organs and systems. According to the International Diabetes Federation (IDF), as of 2021, an estimated 530 million individuals were living with diabetes mellitus globally. Projections suggest that by 2045, this number may surpass 780 million, signaling an alarming increase in the prevalence of the disease. DM's persistent and chronic nature not only affects glucose metabolism but also leads to various complications. Among the more commonly recognized complications are diabetic retinopathy, nephropathy, neuropathy, and cardiovascular disease (CVD). However, what has garnered increasing attention in recent years is the impact of diabetes on the skeletal system. Diabetes mellitus is now known to increase the risk of bone loss and osteoporosis, leading to a heightened vulnerability to fractures [2].

The mechanisms by which diabetes affects bone health are multifaceted and differ significantly between type 1 diabetes mellitus (T1D) and type 2 diabetes mellitus (T2D). T1D primarily exerts its negative effects on bone health by lowering bone mineral density (BMD). The onset of T1D, typically occurring in adolescence, coincides with a crucial period of rapid skeletal development. As a result, those with T1D often experience reduced bone density at an early age, which can exacerbate bone fragility as they age. This early impairment in bone development places T1D patients at higher risk for more severe skeletal consequences later in life. Though T1D's influence on bone health has been recognized for some time, it is T2D that affects a larger proportion of the population. The relationship between T2D and bone health is more complex due to the various metabolic disturbances associated with the condition, including obesity. Obesity, which often coexists with T2D, may itself have detrimental effects on bone quality. Unlike T1D, where BMD is typically reduced, T2D is often associated with normal or even elevated BMD levels. This paradox suggests that other factors, such as bone quality, microarchitectural integrity, and other metabolic influences, may play a more substantial role in the increased fracture risk seen in

* Corresponding author.
E-mail addresses: preetisharma.psit@gmail.com, preeti.sharma@psit.ac.in (P. Sharma).

https://doi.org/10.1016/j.metop.2024.100330
Received 29 September 2024; Received in revised form 6 November 2024; Accepted 7 November 2024
Available online 8 November 2024

Abbreviations

AGEs	Advance glycation end-products
DN	Diabetic Mellitus
TD1M	type 1 diabetes
T2DM	type 2 diabetes
MGO	Methylglyoxal
ROS	Reactive oxygen species
IL-6	Interleukin 6
GLP-1	Glucagon-like peptide-1
GIP	Glucose-dependent insulinotropic polypeptide
TNF	Tumor necrosis factor
CGM	Continuous glucose monitoring (CGM)
MSCs	Mesenchymal stem cells
RANKL	Receptor activator of nuclear factor-kB ligand
CVD	Cardiovascular disease
IDF	International Diabetes Federation
FRAX	Fracture Risk Assessment
BMD	Bone mineral density
DXA	dual-energy X-ray absorptiometry
IGF-1	Insulin-like growth factor 1
HRCT	High-Resolution Computed Tomography
MRI	Magnetic Resonance Imaging
WHO	World Health Organization
CGM	Continuous glucose monitoring
SGLT2	Sodium-glucose co-transporter-2
LPS	lipopolysaccharides

T2D patients [3].

Despite elevated BMD, individuals with T2D are at an increased risk of fractures compared to the general population. This paradox indicates the complex pathophysiological changes that occur in diabetic bone disease, which impair bone quality beyond what is measurable through BMD alone. Furthermore, the risk of falls in individuals with diabetes is heightened, which compounds the danger of fractures. Contributing factors to this elevated fall risk include peripheral neuropathy, poor glycemic control, visual impairments, and the potential side effects of certain diabetes treatments. Addressing bone fragility in diabetic patients is crucial for improving their quality of life and preventing debilitating complications. However, there is a notable lack of robust data on the specific management of bone health in individuals with diabetes. Current treatment approaches for bone fragility in diabetic patients largely mirror those used for non-diabetic populations. Yet, given the unique metabolic profile and disease complications associated with diabetes, these approaches may not be entirely sufficient or tailored to the diabetic population's needs [4].

The societal burden of diabetes extends beyond its effects on the individual. Diabetes significantly reduces quality of life through its associated complications, which can be disabling and life-threatening. Managing diabetes and its complications places a substantial financial strain on healthcare systems worldwide. As such, efforts aimed at early diagnosis, effective treatment, and comprehensive prevention strategies are critical not only to improving patient outcomes but also to reducing the broader economic burden.

Diabetes-related skeletal complications have only recently gained recognition as a critical area of concern. Traditional diabetes complications are generally categorized as either microvascular or macrovascular. Microvascular complications include damage to small blood vessels, leading to conditions such as retinopathy, nephropathy, and neuropathy, while macrovascular complications involve larger vessels, contributing to the development of cardiovascular disease. Over the past few decades, evidence has mounted that bone health should be considered an additional category of diabetes complications. This emerging field of research highlights the need for increased awareness of diabetic bone disease, as well as improved diagnostic and therapeutic strategies to manage bone fragility in diabetic patients [5].

One of the major challenges in managing diabetic bone disease lies in its diagnosis. Conventional methods for assessing fracture risk, such as measuring BMD via dual-energy X-ray absorptiometry (DXA) and using the Fracture Risk Assessment (FRAX) tool, may underestimate fracture risk in individuals with diabetes. This underestimation underscores the importance of developing more accurate assessment tools that account for diabetes-specific risk factors, such as compromised bone quality and the unique effects of hyperglycemia on skeletal tissue [6].

Osteoporosis is a common concern for aging populations and is particularly prevalent in individuals with diabetes. It is defined as a systemic skeletal disorder characterized by decreased bone mass and deterioration of bone microarchitecture, both of which contribute to increased bone fragility and a heightened risk of fractures. The World Health Organization (WHO) classifies osteoporosis based on BMD values, with a T-score of −2.5 or lower indicating the presence of osteoporosis. However, in diabetic patients, this criterion may not fully capture the extent of bone quality deterioration, as other factors, such as changes in bone turnover and the presence of advanced glycation end products (AGEs), play crucial roles in weakening the bone matrix [3].

Diabetic bone disease increases susceptibility to fractures and heightens the risk of chronic pain, motor dysfunction, and disability. Importantly, patients with diabetic bone disease are at an even greater risk of fractures than those with primary osteoporosis, making it a particularly concerning complication of diabetesInsulin, a critical regulator of glucose metabolism, also plays a direct role in bone health. In T1D, insufficient insulin levels impair bone formation, while in T2D, insulin resistance can disrupt normal bone remodeling processes. Moreover, diabetes-associated inflammation and oxidative stress further exacerbate bone damage [7].

This review aims to provide a detailed overview of the current state of knowledge regarding diabetic bone disease, including its epidemiology, pathophysiology, diagnosis, and treatment options, as well as offering insights into future directions for research and clinical practice.

2. Underlying processes in diabetic osteopathy

Diabetic bone disease is characterized 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 AGEs, and the effects of pro-inflammatory cytokines and oxidative stress (see Fig. 1).

2.1. Deficits in insulin and IGF-1 signaling

Insulin and IGF-1 are crucial in maintaining bone health by supporting bone tissue formation and osteoblast function. Insulin promotes DNA synthesis, osteocalcin production, and collagen formation in osteoblasts, all essential for bone formation and remodeling. It also upregulates RUNX2, a gene vital for the differentiation of osteoblasts and the maturation of the bone matrix. In patients with T1DM, the autoimmune destruction of pancreatic β-cells results in an absolute insulin deficiency. This lack of insulin during the critical period of adolescence impairs bone mineralization, leading to persistently low BMD throughout life. Consequently, individuals with T1DM are more prone to fractures and other skeletal complications [8].

In contrast, early-stage T2DM is often associated with insulin resistance, leading to compensatory hyperinsulinemia. During this phase, bone mineralization may be increased due to the high levels of

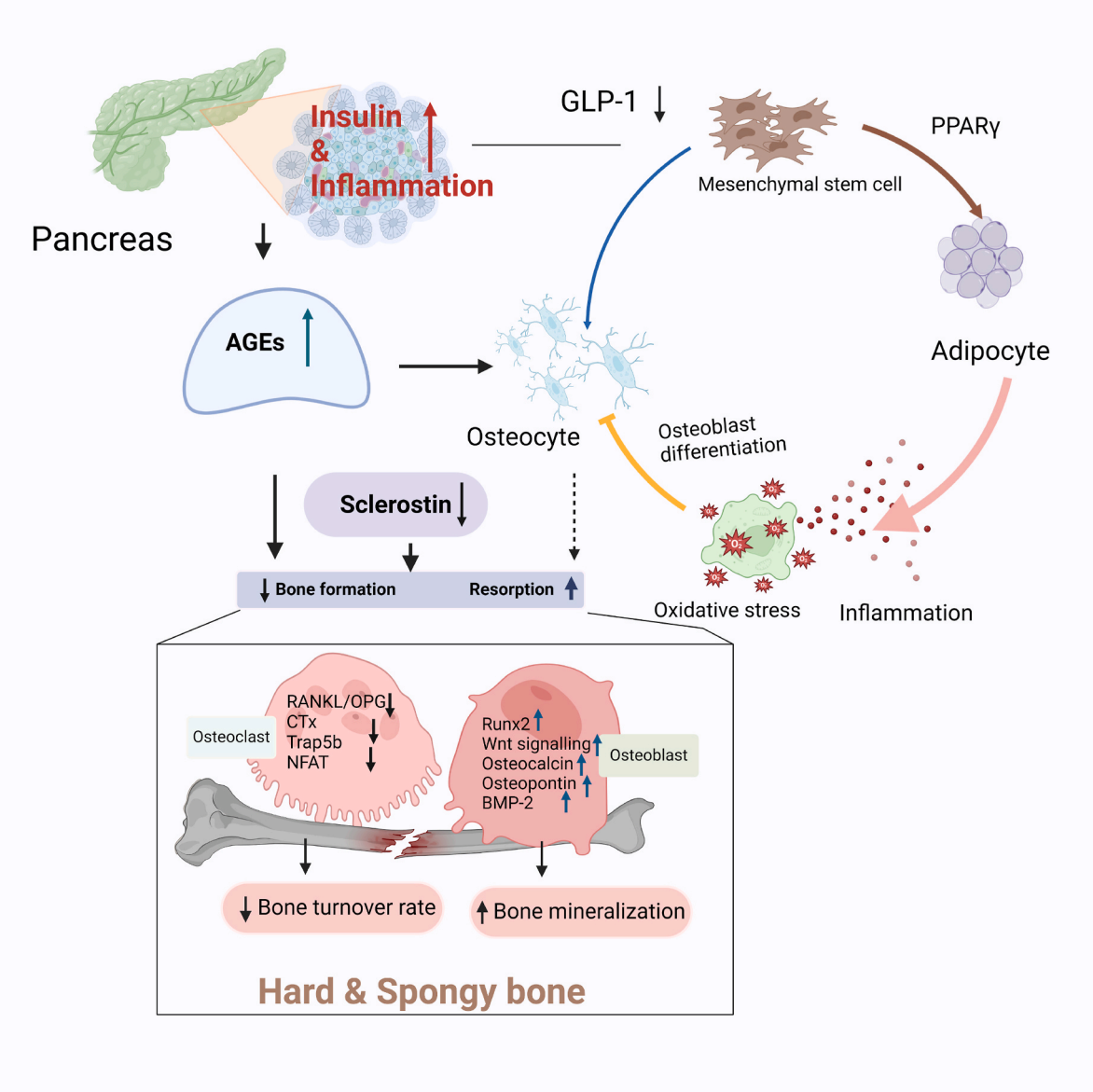


Figure. Illustrated image showed the underlying mechanism of Diabetic osteopathy.

circulating insulin, which exerts anabolic effects on bone tissue. However, as T2DM progresses, insulin secretion declines, reducing the beneficial effects on bone health. Over time, this decline in insulin, combined with metabolic disturbances, leads to a reduction in BMD and an increased risk of fractures. IGF-1, which is structurally similar to insulin, also plays a key role in promoting osteoblast activity and bone matrix mineralization. Diabetic patients often experience decreased levels of IGF-1, which correlates with reduced bone formation and an increased likelihood of fractures [9].

Previous clinical studies have examined BMD and fracture rates in young adults with T1DM through a multicenter cohort study. The results revealed significantly lower BMD in these individuals than non-diabetic controls, especially in the lumbar spine and hip regions. A longitudinal analysis assessed the impact of intensive insulin therapy on bone quality in adolescents with T1DM. Although glycemic control improved with treatment, no significant changes in BMD were observed, indicating that early insulin treatment alone may not sufficiently restore bone health in this population [10].

A randomized controlled trial investigated the effects of vitamin D and calcium supplementation in patients with T1DM. While supplementation enhanced serum markers of bone turnover, there was no significant improvement in BMD over the 12-month study period [11]. Additionally, a study focusing on continuous glucose monitoring (CGM) in postmenopausal women with T1DM found that improved glycemic control via CGM was associated with reduced bone loss. A retrospective analysis covering 10 years revealed an increased risk of hip fractures in patients with T1DM compared to age-matched controls, highlighting the importance of early intervention to reduce fracture risk [12].

For T2DM, a population-based cohort study analyzed fracture risks in older adults. The results indicated that individuals with T2DM had a higher fracture risk despite normal or elevated BMD, underscoring the complexity of diabetic bone disease [13]. A clinical trial explored the effects of metformin on bone health in postmenopausal women with T2DM, suggesting that metformin may provide a protective effect on bone quality and reduce fracture risk [14]. Another study evaluated the impact of sodium-glucose co-transporter-2 (SGLT2) inhibitors on bone health in T2DM patients. While SGLT2 inhibitors improved glycemic control, they were also linked to a modest increase in fracture risk [15]. Additionally, an investigation into GLP-1 receptor agonists revealed that

these drugs might have a neutral or slightly positive effect on bone turnover markers without significantly altering BMD. Finally, a systematic review of thiazolidinediones in T2DM confirmed that these medications are associated with a higher incidence of fractures, particularly in postmenopausal women [16].

These recent studies highlight the complex relationship between diabetes and bone health, emphasizing the need for tailored therapeutic strategies to mitigate fracture risk in both T1DM and T2DM patients.

2.2. Persistent hyperglycemia and advanced glycation

Hyperglycemia, a defining characteristic of diabetes, has a detrimental impact on bone health by directly inhibiting the activity of osteoblasts and osteocytes, the cells responsible for bone formation and maintenance. Elevated glucose levels disrupt normal bone metabolism by reducing the synthesis of extracellular matrix components and slowing down mineralization processes. This impairment results in decreased bone formation and increased bone fragility. Hyperglycemia also promotes the apoptosis (cell death) and senescence (aging) of osteoblasts, further exacerbating bone loss. These factors collectively weaken the bone structure, making it more susceptible to fractures [17].

One of the major contributors to bone fragility in diabetes is the accumulation of AGEs. AGEs are formed when high blood sugar levels lead to the non-enzymatic glycation of proteins, such as collagen, which is a key component of the bone matrix. Over time, AGEs accumulate in bone tissue, leading to the stiffening and weakening of collagen fibers. This reduces the elasticity of collagen, a critical factor in maintaining bone's ability to absorb mechanical stress. The resulting loss of flexibility increases bone brittleness and elevates the risk of fractures, particularly in individuals with long-standing diabetes. AGEs also have a profound effect on the cellular level of bone metabolism. They inhibit the differentiation of osteoblasts, the cells responsible for new bone formation, and decrease the expression of alkaline phosphatase, an enzyme essential for bone mineralization. This reduction in osteoblast activity further diminishes bone formation, contributing to a decrease in bone mass and quality. As a result, the accumulation of AGEs, coupled with hyperglycemia-induced cellular dysfunction, plays a significant role in the development of diabetic bone disease and the heightened fracture risk observed in diabetic patients [18].

A clinical trial focusing on young adults with T1DM assessed the long-term effects of hyperglycemia on bone quality. The study revealed that patients with poor glycemic control exhibited significantly higher levels of AGEs in their bone tissue, which resulted in reduced bone strength. Another investigation explored the relationship between AGEs and fracture risk in T1DM patients, finding that elevated serum AGE levels were linked to an increased risk of non-vertebral fractures, independent of BMD. A cross-sectional study examined the impact of hyperglycemia on osteoblast function among T1DM patients. The findings indicated that chronic hyperglycemia impaired osteoblast activity and markedly slowed bone formation rates. Additionally, a longitudinal cohort study measured bone turnover markers in T1DM patients with varying levels of glycemic control, showing that those with consistently high glucose levels had increased markers of bone resorption and decreased markers of bone formation. A retrospective analysis assessed the influence of intensive glucose control on bone health in T1DM patients, suggesting that tighter glucose management over time was associated with reduced AGE accumulation and improved mechanical properties of bone [19].

In a similar vein, a study examining postmenopausal women with T2DM found that hyperglycemia significantly contributed to AGE accumulation in bone collagen, resulting in higher fracture rates despite normal or elevated BMD. A clinical trial evaluating the long-term effects of metformin use on AGE levels in T2DM patients indicated that metformin lowered AGE accumulation, indirectly enhancing bone quality and reducing fracture risk. Another study conducted on elderly T2DM patients demonstrated a correlation between higher serum AGE levels and increased hip fracture risk, suggesting that AGE measurement could serve as a predictive marker for fracture risk. Additionally, a randomized controlled trial tested the effects of AGE inhibitors on bone health in T2DM patients, revealing a reduction in bone brittleness and an improvement in bone elasticity after 12 months of treatment. Finally, this study investigated the relationship between hyperglycemia and bone mineral density in T2DM, finding that patients with poor glycemic control had lower bone formation rates and increased cortical porosity, which contributed to their higher fracture risk [20].

These studies highlight the critical role that hyperglycemia and AGEs play in disrupting bone metabolism and increasing fracture risk in diabetic patients. Both T1DM and T2DM populations suffer from these metabolic derangements, emphasizing the importance of tight glycemic control and therapeutic strategies aimed at reducing AGE accumulation to preserve bone health.

2.3. Inflammatory signaling molecules and reactive oxygen species (ROS)

Chronic inflammation and oxidative stress are key contributors to the development of diabetic bone disease. In diabetes, prolonged inflammation is marked by elevated levels of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6). These cytokines play a significant role in disrupting normal bone remodeling by promoting the activity of osteoclasts, the cells responsible for bone resorption. TNF-α, in particular, stimulates the differentiation of osteoclast precursors into mature osteoclasts, thereby accelerating the breakdown of bone tissue. This heightened osteoclast activity leads to an imbalance between bone resorption and bone formation, resulting in net bone loss [21].

IL-6 further exacerbates this process by promoting the differentiation of osteoclasts and degrading the bone matrix. As bone remodeling is a tightly regulated process, the overactivity of osteoclasts, driven by these inflammatory cytokines, leads to excessive bone resorption, making bones more fragile and susceptible to fractures. In addition to inflammation, diabetes also induces oxidative stress, primarily through the generation of excessive ROS. Hyperglycemia and chronic inflammation both contribute to elevated ROS levels, which negatively affect bone health [22]. ROS can damage various cell types, including bone marrow mesenchymal stem cells (MSCs), which are essential for new bone formation. The apoptosis (programmed cell death) of these MSCs impairs their ability to differentiate into osteoblasts, the cells responsible for bone synthesis. This reduction in osteoblast activity results in decreased bone formation, further contributing to the progression of diabetic bone disease. Oxidative stress also disrupts the signaling pathways involved in bone metabolism, leading to an imbalance that favors bone loss. The combined effects of chronic inflammation and oxidative stress create a harmful environment for bone health in diabetic patients, increasing their risk of osteoporosis and fractures [23,24].

Previous clinical studies have indicated that research on young adults with T1DM revealed elevated levels of pro-inflammatory cytokines TNF-α and IL-6 in the blood. These elevated levels correlated with increased markers of bone resorption and decreased BMD, suggesting a direct link between inflammation and bone loss [25]. Researchers also explored the effects of anti-TNF therapy in T1DM patients with low bone mass, finding that treatment reduced osteoclast activity and slowed down bone resorption, demonstrating potential for therapeutic intervention [26]. A clinical trial examining oxidative stress markers in adolescents with T1DM found that patients with poor glycemic control had significantly higher levels of reactive oxygen species (ROS), which were associated with reduced osteoblast activity and impaired bone formation. Furthermore, this study assessed the impact of IL-6 inhibitors on bone health in T1DM patients, revealing that these inhibitors reduced bone resorption and improved bone turnover markers, indicating a positive effect on bone remodeling. A prospective study investigated the relationship between ROS and MSC apoptosis in T1DM patients, showing that elevated oxidative stress contributed to reduced MSC

viability and impaired bone formation [9,27].

Similarly, for T2DM, a population-based study measured cytokine levels in elderly patients and found a strong association between elevated IL-6 levels and increased fracture risk, despite normal BMD levels. A clinical trial evaluated the use of antioxidants to reduce oxidative stress in T2DM patients, demonstrating that antioxidant supplementation lowered ROS levels and improved markers of bone formation. Another study investigating the role of TNF-α in bone health found that higher TNF-α levels were associated with increased osteoclast activity and higher bone resorption rates in T2DM patients. Researchers tested the efficacy of anti-inflammatory drugs in improving bone quality in postmenopausal women with T2DM, observing that treatment reduced both TNF-α and IL-6 levels, leading to improved bone density and reduced fracture risk. A longitudinal study explored the impact of oxidative stress on fracture risk in T2DM patients, revealing that higher ROS levels were significant predictors of future fractures, emphasizing the importance of managing oxidative stress in diabetes care [28,29].

These studies highlight the critical role of pro-inflammatory cytokines and oxidative stress in disrupting bone metabolism in diabetic patients. Both T1DM and T2DM populations experience significant bone loss due to chronic inflammation and elevated ROS levels, underscoring the need for therapies that target these pathways to prevent fractures and improve bone health.

2.4. Bone turnover

Bone turnover, the dynamic process of bone remodeling involving the balanced activities of bone resorption and formation, is crucial for maintaining bone strength and quality. In diabetes, this balance is often disrupted, leading to impaired bone quality and increased fracture risk, even when bone density appears normal. The underlying mechanisms of bone turnover in diabetic bone disease involve interactions between hyperglycemia, AGEs, inflammation, and hormonal imbalances. Hyperglycemia, a hallmark of diabetes, contributes to the formation of AGEs, which accumulate in bone collagen, making it more brittle and less resilient. These changes impair the biomechanical properties of bone, leading to an increased susceptibility to fractures. Additionally, chronic inflammation associated with diabetes further disrupts the bone remodeling by increasing bone resorption and reducing bone formation. Hormonal imbalances, particularly involving insulin and osteocalcin, also play a role, as insulin deficiency or resistance affects osteoblast function, reducing bone formation. Interestingly, studies have shown higher serum levels of sclerostin in patients with Type 1 and Type 2 diabetes compared to controls. Sclerostin, a bone-signaling peptide secreted by osteocytes, inhibits osteoblast activity by blocking the canonical Wnt signaling pathway and stimulates osteoclast activation by promoting the release of receptor activator of nuclear factor-kB ligand (RANKL) from osteocytes. Secretion of sclerostin by osteocytes is typically reduced by mechanical loading; however, women with Type 2 diabetes and relative immobility have shown increased sclerostin levels. *In vitro* studies further support this, demonstrating increased sclerostin expression in osteoblasts, osteocytes, and osteocyte-like cells after incubation with high glucose concentrations. This altered bone turnover process is a key contributor to the higher incidence of fractures in diabetic patients, despite often normal or slightly elevated BMD. Below is a summary of key clinical studies that have examined bone turnover in the context of diabetic bone disease. These studies underscore the multifaceted nature of bone turnover disruptions in diabetic bone disease [30,31].

For example, Krakauer et al. (2012) observed a significant imbalance in bone turnover markers among patients with T1DM, noting decreased bone formation and increased resorption, which suggests a net loss of bone quality over time. This finding is critical as it indicates that even in the absence of overt osteoporosis, diabetic patients may still experience compromised bone integrity. Similarly, Napoli et al. (2013) highlighted how hyperglycemia promotes the formation of AGEs within bone tissue, which directly weakens the structural properties of the bone. The relationship between insulin resistance and bone turnover was further explored by Shu et al. (2015), who identified reduced osteoblast activity as a key factor in diminished bone formation among patients with T2DM. In addition to these metabolic factors, chronic inflammation has been shown to exacerbate disruptions in bone turnover, as demonstrated by Hamann et al. (2016). Inflammatory cytokines like TNF-α and IL-6, elevated in diabetic patients, can increase osteoclast activity, leading to excessive bone resorption. Lastly, Hofbauer et al. (2018) focused on the role of osteocalcin, a hormone produced by osteoblasts found that its reduced levels in diabetic patients correlate with lower bone formation and a higher risk of fractures. A study on bone turnover markers in young adults with T1DM revealed that hyperglycemia promotes the accumulation of AGEs, resulting in reduced bone strength despite normal BMD. Another clinical trial investigated the role of sclerostin in T1DM patients and found that elevated levels correlated with decreased bone formation and increased resorption, indicating disrupted bone turnover. Additionally, researchers examined the effects of insulin therapy on bone turnover in T1DM patients, discovering that intensive insulin therapy improved osteoblast function and bone formation markers, although resorption remained elevated due to persistent inflammation [9,32,33].

Furthermore, a study measuring the influence of hyperglycemia on inflammatory cytokines in T1DM patients showed that elevated IL-6 levels were strongly associated with increased bone resorption and lower bone formation rates. A longitudinal cohort study investigated fracture risk in T1DM patients, emphasizing that long-term hyperglycemia, sclerostin levels, and inflammatory markers together contributed to an increased incidence of fractures, despite normal or slightly elevated BMD. In similar research related to T2DM, investigators studied the role of insulin resistance in postmenopausal women, finding that it led to diminished osteoblast function and lower bone formation, despite the paradoxically high BMD often observed in these patients. Another study examined the relationship between AGE accumulation and bone fragility in elderly T2DM patients, highlighting that AGEs impaired bone matrix quality, leading to an increased risk of fractures. A clinical trial assessed the effects of anti-sclerostin antibodies on bone turnover in T2DM patients, demonstrating that targeting sclerostin reduced osteoclast activity and improved bone formation rates. Researchers also explored the role of oxidative stress in T2DM-induced bone disease, showing that elevated ROS levels contributed to osteoblast apoptosis, further impairing bone formation. Finally, a randomized controlled trial evaluated the impact of metformin on bone turnover in T2DM patients, with results indicating that metformin improved osteoblast function and decreased osteoclast activity by reducing inflammation and ROS levels [9,26,34].

These studies underscore the multifaceted nature of bone turnover disruptions in diabetic bone disease, driven by hyperglycemia, inflammation, AGEs, and hormonal imbalances. Addressing these underlying factors is critical to managing fracture risk in diabetic patients, emphasizing the need for a comprehensive approach to treatment beyond focusing solely on BMD.

Collectively, these studies reveal that diabetic bone disease is driven by complex and interrelated mechanisms that disrupt normal bone turnover, making it essential to address these factors in managing fracture risk in diabetic patients.

2.5. Bone material properties

Bone material properties, such as bone strength, elasticity, and microarchitecture, are crucial in determining overall bone quality. In the context of diabetes, these properties are often compromised due to underlying mechanisms that alter the bone matrix and microstructure, increasing fracture risk even when BMD is normal. One key factor is the accumulation of AGE in the bone collagen matrix, which makes the bone more brittle and prone to fractures. Hyperglycemia, a common feature

of diabetes, accelerates the formation of AGEs, leading to cross-linking of collagen fibers and decreased bone toughness. Additionally, chronic inflammation and oxidative stress in diabetes further degrade bone quality by increasing bone resorption and impairing bone formation. These processes result in changes to the bone's microarchitecture, reducing its ability to absorb mechanical forces and increasing the likelihood of fractures. Studies have also shown that altered bone material properties in diabetes may not be fully captured by standard BMD measurements, highlighting the importance of assessing bone quality beyond density alone [31].

2.6. Gastroenteric hormones

The relationship between gastrointestinal hormones and bone metabolism in diabetes is an emerging area of research that has garnered increasing attention over the past decade. Diabetes, particularly Type 2 diabetes, is known to influence various aspects of bone health, including bone density, strength, and healing. The interplay between gastrointestinal hormones and bone metabolism in diabetic patients is complex, involving hormones such as glucagon-like peptide-1 (GLP-1), glucose-dependent insulinotropic polypeptide (GIP), and ghrelin. These hormones, which are primarily known for their roles in glucose regulation and appetite control, have also been shown to influence bone remodeling processes. This is particularly relevant for patients with diabetes, where altered hormone levels may contribute to an increased risk of osteoporosis and fractures. Below is a summary of key clinical studies that have explored the role of gastrointestinal hormones in bone health among diabetic patients [35].

Mainly these studies underscore the significance of gastrointestinal hormones in the regulation of bone health, particularly in the context of diabetes. For example, GLP-1, a hormone primarily involved in enhancing insulin secretion and slowing gastric emptying, has also been shown to play a crucial role in bone metabolism. Clinical trials with GLP-1 receptor agonists have demonstrated reductions in bone resorption markers, suggesting a protective effect against bone loss in diabetic patients. This is particularly important given that individuals with diabetes are at an increased risk for osteoporosis and fractures, and traditional bone health management strategies may not be as effective in this population. Similarly, GIP, another incretin hormone, has been found to promote bone formation and enhance bone density. Studies have shown that GIP's bone-protective effects may be particularly beneficial in reducing fracture risk among diabetic patients, a group that often experiences impaired bone healing and increased fracture rates. Ghrelin, known for its role in stimulating appetite, has also been identified as a positive regulator of bone formation, particularly in the context of diabetic osteoporosis. These findings suggest that therapies targeting these gastrointestinal hormones could potentially offer new avenues for preventing and treating bone complications in diabetes. Furthermore, the combination of GLP-1 and GIP therapies has shown promise in improving overall bone health in diabetic patients, offering a potential dual benefit of managing blood glucose levels and enhancing bone strength. The accelerated fracture healing observed in patients receiving GLP-1 and GIP analogs further supports the potential of these hormones in addressing the unique challenges faced by diabetic patients concerning bone health [36–38].Overall, these studies suggest that these hormones could be key targets for novel therapeutic approaches to prevent and manage bone complications in diabetic patients.

2.7. Microvascular issues

Microvascular complications are among the most critical issues faced by individuals with diabetes, significantly impacting both their quality of life and long-term health outcomes. In recent years, research has increasingly focused on understanding how diabetes affects bone health, particularly in relation to microvascular complications. Several clinical studies have explored the intricate link between bone health and diabetes, revealing that microvascular complications, such as diabetic retinopathy, nephropathy, and neuropathy, may also extend their detrimental effects on bone tissue. These complications can lead to a range of bone disorders, including osteoporosis, increased fracture risk, and impaired bone healing. This growing body of research underscores the importance of early detection and management of these complications to prevent severe bone-related outcomes in diabetic patients. Below is a summary of key clinical studies that have contributed to our understanding of microvascular complications in bone diabetes [39,40].

2.8. Gut microbiota

Gut microbiota, the diverse population of microorganisms residing in the human gastrointestinal tract, plays a critical role in overall health, including metabolism, immunity, and even bone health [41]. Emerging research has highlighted a strong link between gut microbiota dysbiosis and metabolic diseases like diabetes. Alterations in the gut microbiome can exacerbate diabetic complications, including those affecting bone health. Diabetic bone disease, characterized by impaired bone quality and increased fracture risk, is now being explored in the context of gut microbiota.

In healthy individuals, gut microbiota influences bone health by regulating nutrient absorption, modulating immune responses, and producing metabolites that affect bone metabolism. Short-chain fatty acids (SCFAs), such as butyrate, propionate, and acetate, are produced by bacterial fermentation of dietary fiber in the colon. SCFAs have been shown to enhance calcium absorption in the intestines and promote bone formation by stimulating osteoblast activity. Butyrate, in particular, has anti-inflammatory properties that can counteract the pro-inflammatory environment associated with diabetes. However, in diabetic individuals, gut microbiota composition shifts towards a dysbiotic state, reducing the production of beneficial SCFAs and increasing harmful metabolites that contribute to bone degradation[42–44].

Diabetes, both T1DM and T2DM, is associated with increased intestinal permeability, commonly referred to as "leaky gut." This condition allows endotoxins, such as lipopolysaccharides (LPS), to enter the bloodstream, triggering systemic inflammation. Chronic inflammation is a hallmark of diabetes and is closely linked to bone turnover disruption. Pro-inflammatory cytokines, like TNF-α and IL-6, stimulated by LPS, further promote osteoclast activity, leading to increased bone resorption and reduced bone formation. Dysbiosis of the gut microbiota amplifies this process by exacerbating systemic inflammation and oxidative stress, which are detrimental to bone health. In recent years, several clinical studies have investigated the connection between gut microbiota, diabetes, and bone health. One significant study conducted in 2019 examined gut microbiota composition in T1DM patients and found that the abundance of beneficial bacteria, such as *Bifidobacterium* and *Lactobacillus*, was reduced. These bacteria are known for producing SCFAs and maintaining intestinal barrier function. The study concluded that gut dysbiosis in T1DM patients contributed to systemic inflammation and bone loss[45–47].

In T2DM, a 2020 study analyzed the effects of a high-fiber diet on gut microbiota and bone turnover. The researchers found that increasing dietary fiber led to higher SCFA production, which was associated with improved bone density and a decrease in bone resorption markers. Another study in 2021 investigated the role of probiotics in modulating bone health in T2DM patients. Probiotic supplementation increases the abundance of SCFA-producing bacteria, leading to enhanced calcium absorption and reduced inflammatory cytokines, which are critical in preventing bone loss. More recently, a 2022 study explored the gut-bone axis in diabetic mice models, demonstrating that dysbiosis led to decreased bone strength and altered bone microarchitecture. The researchers also found that restoring gut microbiota balance through prebiotic and probiotic interventions reversed these negative effects on bone health. Another 2023 clinical trial on T2DM patients revealed that synbiotics (a combination of probiotics and prebiotics) improved both

metabolic control and bone turnover, further emphasizing the importance of healthy gut microbiota for maintaining bone integrity in diabetic individuals [42,48].

In conclusion, gut microbiota plays an essential role in bone metabolism, and its dysregulation in diabetes contributes to the pathogenesis of diabetic bone disease. Alterations in the gut microbiome, characterized by reduced SCFA production and increased systemic inflammation, disrupt normal bone remodeling, leading to increased fracture risk. Restoring gut microbiota balance through dietary interventions, probiotics, and prebiotics offers a promising approach to improving bone health in diabetic patients.

2.9. Effects on various bone types

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

2.9.1. Compact bone

Compact or cortical bone constitutes about 80 % of the skeletal mass and provides strength and support. Its dense and solid structure characterizes it. In diabetes, cortical bone is particularly vulnerable due to altered bone remodeling processes. Clinical research indicates that diabetes increased increases cortical bone fragility, despite normal BMD. This paradox is partly due to the impaired quality of cortical bone in diabetic patients. Studies have shown that AGEs accumulate in the collagen matrix of cortical bone, reducing collagen elasticity and mechanical properties. For instance, Sellmeyer et al. (2010) found that AGEs in cortical bone significantly diminish bone toughness, increasing the risk of fractures. Additionally, diabetes-induced inflammation and oxidative stress further compromise cortical bone integrity by enhancing bone resorption and decreasing bone formation [18].

2.9.2. Spongy bone

Spongy or Trabecular bone is found mainly in the interior of bones and is responsible for supporting and distributing mechanical loads. It has a porous, lattice-like structure that is more metabolically active compared to cortical bone. In diabetic patients, trabecular bone is also adversely affected, though the mechanisms differ slightly from those impacting cortical bone. Research has shown that diabetes leads to trabecular bone loss due to increased osteoclast activity and reduced osteoblast function. For example, studies by Farlay et al. (2013) demonstrated that diabetes causes alterations in trabecular microarchitecture, including reduced trabecular number and connectivity, which compromises bone strength and increases fracture risk. Hyperglycemia and elevated AGEs contribute to these changes by impairing the formation of new trabecular bone and enhancing bone resorption [49,50].

Moreover, diabetes-related alterations in bone metabolism decrease the ability to maintain trabecular bone density. The imbalance between bone resorption and formation, exacerbated by chronic inflammation and oxidative stress, accelerates the deterioration of trabecular bone quality [51]. Research by Kanis et al. (2015) highlighted that diabetic patients often show a significant loss of trabecular bone, contributing to increased fracture risk even in the presence of normal BMD values.

3. Diagnostic tools for diabetic bone disease

Diagnosing diabetic bone disease involves assessing bone quality and integrity through various diagnostic tools. Imaging techniques and biomarkers are essential for evaluating bone health in diabetic patients.

3.1. Imaging techniques

1. **Dual-Energy X-ray Absorptiometry (DXA):** DXA is the gold standard for measuring BMD, providing a quantitative assessment of bone density at key sites like the hip and spine. While DXA is useful for detecting osteoporosis, it may not fully capture changes in bone quality associated with diabetes [52].
2. **High-Resolution Computed Tomography (HRCT):** HRCT offers detailed images of bone microarchitecture, including trabecular and cortical bone. Studies, such as those by Farlay et al. (2013), have shown that HRCT can identify trabecular bone loss and structural changes, which are critical in assessing diabetic bone disease [53].
3. **Magnetic Resonance Imaging (MRI):** MRI can visualize bone marrow and soft tissues, detecting bone marrow edema and structural abnormalities associated with diabetes.

4. Future directions

Potential therapeutic advances in managing bone diabetes include novel drug therapies, such as selective RANKL inhibitors and bone-forming agents like sclerostin antibodies, which may offer targeted benefits for improving bone density and strength [54]. Research into gut microbiota modulation through probiotics and prebiotics holds promise for enhancing bone health by reducing inflammation and improving nutrient absorption. Additionally, advancements in personalized medicine, incorporating genetic and biochemical profiles, could tailor interventions more effectively. Emerging technologies, such as high-resolution imaging and bone biomarkers, are enhancing early diagnosis and monitoring, potentially transforming the management of diabetic bone disease.

5. Conclusion

In conclusion, managing diabetic bone disease requires a multifaceted approach integrating pharmacological interventions, lifestyle modifications, dietary adjustments, and emerging therapeutic insights. Pharmacological treatments, including bisphosphonates, denosumab, and teriparatide, effectively target bone resorption and formation, while novel anti-diabetic medications like GLP-1 agonists offer additional benefits. Lifestyle changes, such as regular physical activity and smoking cessation, are crucial for maintaining bone health. Adequate nutrition, including calcium and vitamin D, supports bone density. Recent research highlights the role of gut microbiota in bone health, suggesting the potential for probiotics and prebiotics to improve outcomes. Advances in diagnostic tools, including imaging and biomarkers, further enhance the ability to monitor and manage bone health in diabetic patients. Together, these strategies offer a comprehensive approach to reducing fracture risk and improving bone health in diabetes.

CRediT authorship contribution statement

Preeti Sharma: Writing – review & editing, Writing – original draft, Software, Data curation, Conceptualization. **Rahul Kumar Sharma:** Writing – review & editing, Supervision. **Khushboo Gaur:** Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] Bailey CJ, Day C. The future of new drugs for diabetes management. Diabetes Res Clin Pract 2019;155.

[2] New estimates indicate that more than 1.3 billion people could be living with diabetes by 2050 - International Diabetes Federation n.d. https://idf.org/news/gbd-estimates-2021/(accessed September 22, 2024).

[3] Liu T, Wang Y, Qian B, Li P. Potential metabolic pathways involved in osteoporosis and evaluation of fracture risk in individuals with diabetes. BioMed Res Int 2024; 2024:6640796. https://doi.org/10.1155/2024/6640796.

[4] Lv Z, Cai X, Bian Y, Wei Z, Zhu W, Zhao X, et al. Advances in mesenchymal stem cell therapy for osteoarthritis: from preclinical and clinical perspectives. Bioengineering 2023;10:195. https://doi.org/10.3390/BIOENGINEERING10020195. 2023;10:195.

[5] Li Y, Liu YY, Liu S, Gao M, Wang W, Chen K, et al. Diabetic vascular diseases: molecular mechanisms and therapeutic strategies. Signal Transduct Targeted Ther 2023;8(1):1–29. https://doi.org/10.1038/s41392-023-01400-z. 2023;8.

[6] Giha HA, Sater MS, Alamin OAO. Diabetes mellitus tendino-myopathy: epidemiology, clinical features, diagnosis and management of an overlooked diabetic complication. Acta Diabetol 2022;59:871–83.

[7] Gao Q, Jiang Y, Zhou D, Li G, Han Y, Yang J, et al. Advanced glycation end products mediate biomineralization disorder in diabetic bone disease. Cell Rep Med 2024;5:101694. https://doi.org/10.1016/J.XCRM.2024.101694.

[8] Ruan X, Jin X, Sun F, Pi J, Jinghu Y, Lin X, et al. IGF signaling pathway in bone and cartilage development, homeostasis, and disease. FASEB (Fed Am Soc Exp Biol) J 2024;38. https://doi.org/10.1096/FJ.202401298R.

[9] Meier C, Eastell R, Pierroz DD, Lane NE, Al-Daghri N, Suzuki A, et al. Biochemical markers of bone fragility in patients with diabetes. J Clin Endocrinol Metab 2023; 108:e923–36. https://doi.org/10.1210/CLINEM/DGAD255.

[10] Napoli N, Schwartz AV, Schafer AL, Vittinghoff E, Cawthon PM, Parimi N, et al. Vertebral fracture risk in diabetic elderly men: the MrOS study. J Bone Miner Res 2018;33:63. https://doi.org/10.1002/JBMR.3287.

[11] Lerchbaum E, Trummer C, Theiler-Schwetz V, Kollmann M, Wölfler M, Pilz S, et al. Effects of vitamin D supplementation on bone turnover and bone mineral density in healthy men: a post-hoc analysis of a randomized controlled trial. Nutrients 2019; 11. https://doi.org/10.3390/NU11040731.

[12] Allen NA, Litchman ML, Chamberlain J, Grigorian EG, Iacob E, Berg CA. Continuous glucose monitoring data sharing in older adults with type 1 diabetes: pilot intervention study. JMIR Diabetes 2022;7:e35687. https://doi.org/10.2196/35687.

[13] Papaioannou I, Pantazidou G, Kokkalis Z, Georgopoulos N, Jelastopulu E. Systematic review: are the elderly with diabetes mellitus type 2 prone to fragility fractures? Cureus 2021;13. https://doi.org/10.7759/CUREUS.14514.

[14] Bahrambeigi S, Yousefi B, Rahimi M, Shafiei-Irannejad V. Metformin; an old antidiabetic drug with new potentials in bone disorders. Biomed Pharmacother 2019;109:1593–601. https://doi.org/10.1016/J.BIOPHA.2018.11.032.

[15] Ha KH, Kim DJ, Choi YJ. Sodium–glucose cotransporter 2 inhibitors do not increase the risk of fractures in real-world clinical practice in Korea: a national observational cohort study. J Diabetes Investig 2022;13:986. https://doi.org/10.1111/JDI.13768.

[16] Daniilopoulou I, Vlachou E, Lambrou GI, Ntikoudi A, Dokoutsidou E, Fasoi G, et al. The impact of GLP1 agonists on bone metabolism: a systematic review. Medicina (B Aires) 2022;58. https://doi.org/10.3390/MEDICINA58020224.

[17] Committee ADAPP. 2. Classification and diagnosis of diabetes: standards of medical care in diabetes—2022. Diabetes Care 2022;45:S17–38. https://doi.org/10.2337/DC22-S002.

[18] Chen W, Mao M, Fang J, Xie Y, Rui Y. Fracture risk assessment in diabetes mellitus. Front Endocrinol 2022;13. https://doi.org/10.3389/FENDO.2022.961761.

[19] Khalid M, Petroianu G, Adem A. Advanced glycation end products and diabetes mellitus: mechanisms and perspectives. Biomolecules 2022;12.

[20] Wu B, Fu Z, Wang X, Zhou P, Yang Q, Jiang Y, et al. A narrative review of diabetic bone disease: characteristics, pathogenesis, and treatment. Front Endocrinol 2022; 13. https://doi.org/10.3389/FENDO.2022.1052592.

[21] Nita M, Grzybowski A. The role of the reactive oxygen species and oxidative stress in the pathomechanism of the age-related ocular diseases and other pathologies of the anterior and posterior eye segments in adults. Oxid Med Cell Longev 2016; 2016:3164734.

[22] Kany S, Vollrath JT, Relja B. Cytokines in inflammatory disease. Int J Mol Sci 2019; 20:6008. https://doi.org/10.3390/IJMS20236008. 2019;20:6008.

[23] Jiang RH, Xu JJ, Zhu DC, Li JF, Zhang CX, Lin N, et al. Glycyrrhizin inhibits osteoarthritis development through suppressing the PI3K/AKT/NF-κB signaling pathway: in vivo and in vitro. Food Funct 2020;11:2126–36. https://doi.org/10.1039/c9fo02241d.

[24] Grässel S, Muschter D. Recent advances in the treatment of osteoarthritis. F1000Res 2020;9. https://doi.org/10.12688/F1000RESEARCH.22115.1.

[25] Huang Z, Xu Z, Wan R, Hu D, Huang Y. Associations between blood inflammatory markers and bone mineral density and strength in the femoral neck: findings from the MIDUS II study. Sci Rep 2023;13(1):1–10. https://doi.org/10.1038/s41598-023-37377-6. 2023;13.

[26] Kawai VK, Stein CM, Perrien DS, Griffin MR. Effects of anti-tumor necrosis factor α (anti-TNF) agents on bone. Curr Opin Rheumatol 2012;24:576. https://doi.org/10.1097/BOR.0B013E328356D212.

[27] Wagner KH, Schwingshackl L, Draxler A, Franzke B. Impact of dietary and lifestyle interventions in elderly or people diagnosed with diabetes, metabolic disorders, cardiovascular disease, cancer and micronutrient deficiency on micronuclei frequency – a systematic review and meta-analysis. Mutation Research/Reviews in Mutation Research 2021;787:108367. https://doi.org/10.1016/J.MRREV.2021.108367.

[28] Romero-Díaz C, Duarte-Montero D, Gutiérrez-Romero SA, Mendivil CO. Diabetes and bone fragility. Diabetes Therapy 2021;12:71. https://doi.org/10.1007/S13300-020-00964-1.

[29] Burgos-Morón E, Abad-Jiménez Z, de Marañón AM, Iannantuoni F, Escribano-López I, López-Domènech S, et al. Relationship between oxidative stress, ER stress, and inflammation in type 2 diabetes: the battle continues. J Clin Med 2019;8.

[30] Meier C, Eastell R, Pierroz DD, Lane NE, Al-Daghri N, Suzuki A, et al. Biochemical markers of bone fragility in patients with diabetes. J Clin Endocrinol Metab 2023; 108:e923. https://doi.org/10.1210/CLINEM/DGAD255.

[31] Monahan GE, Schiavi-Tritz J, Britton M, Vaughan TJ. Longitudinal alterations in bone morphometry, mechanical integrity and composition in Type-2 diabetes in a Zucker diabetic fatty (ZDF) rat. Bone 2023;170:116672. https://doi.org/10.1016/J.BONE.2023.116672.

[32] Safarova S. Evaluation of bone turnover in patients with type 1 diabetes mellitus. J Endocrinol Metab 2018;8:2–5. https://doi.org/10.14740/JEM.V8I1.483.

[33] Martínez-Montoro JI, García-Fontana B, García-Fontana C, Muñoz-torres M. Evaluation of quality and bone microstructure alterations in patients with type 2 diabetes: a narrative review. J Clin Med 2022;11:2206. https://doi.org/10.3390/JCM11082206.

[34] Vavanikunnel J, Sewing L, Triantafyllidou M, Steighardt A, Baumann S, Egger A, et al. Determinants of low bone turnover in type 2 diabetes-the role of PTH. Calcif Tissue Int 2022;111:587. https://doi.org/10.1007/S00223-022-01022-7.

[35] Liu H, Xiao H, Lin S, Zhou H, Cheng Y, Xie B, et al. Effect of gut hormones on bone metabolism and their possible mechanisms in the treatment of osteoporosis. Front Pharmacol 2024;15:1372399. https://doi.org/10.3389/FPHAR.2024.1372399/BIBTEX.

[36] Fisman EZ, Tenenbaum A. The dual glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor agonist tirzepatide: a novel cardiometabolic therapeutic prospect. Cardiovasc Diabetol 2021;20:225. https://doi.org/10.1186/S12933-021-01412-5.

[37] Vyavahare SS, Mieczkowska A, Flatt PR, Chappard D, Irwin N, Mabilleau G. GIP analogues augment bone strength by modulating bone composition in diet-induced obesity in mice. Peptides (NY) 2020;125:170207. https://doi.org/10.1016/J.PEPTIDES.2019.170207.

[38] Hansen MS, Søe K, Christensen LL, Fernandez-Guerra P, Hansen NW, Wyatt RA, et al. GIP reduces osteoclast activity and improves osteoblast survival in primary human bone cells. Eur J Endocrinol 2023;188. https://doi.org/10.1093/EJENDO/LVAC004.

[39] Grover A, Sharma K, Gautam S, Gautam S, Gulati M, Singh SK. Diabetes and its complications: therapies available, anticipated and aspired. Curr Diabetes Rev 2021;17:397–420.

[40] Daamouch S, Emini L, Rauner M, Hofbauer LC. MicroRNA and diabetic bone disease. Curr Osteoporos Rep 2022;20:194. https://doi.org/10.1007/S11914-022-00731-0.

[41] Upadhyay P, Gupta S. Dual mode of Triphala in the reversal of cognition through gut restoration in antibiotic mediated prolonged dysbiosis condition in 5XFAD mice. Exp Neurol 2023:114473.

[42] Di Vincenzo F, Del Gaudio A, Petito V, Lopetuso LR, Scaldaferri F. Gut microbiota, intestinal permeability, and systemic inflammation: a narrative review. Intern Emerg Med 2024;19:275–93. https://doi.org/10.1007/S11739-023-03374-W/FIGURES/2.

[43] Sahu N, Upadhyay P, Mishra SK. In: Tripathi AK, Kotak M, editors. Role of short-chain fatty acids from gut microbiota in neuroendocrine pathogenesis management BT - gut microbiome in neurological health and disorders. Singapore: Springer Nature Singapore; 2022. p. 139–51. https://doi.org/10.1007/978-981-19-4530-4_9.

[44] Ahmed B, Sultana R, Greene MW. Adipose tissue and insulin resistance in obese. Biomed Pharmacother 2021;137:111315. https://doi.org/10.1016/J.BIOPHA.2021.111315.

[45] Larraufie P, Martin-Gallausiaux C, Lapaque N, Dore J, Gribble FM, Reimann F, et al. SCFAs strongly stimulate PYY production in human enteroendocrine cells. Sci Rep 2018;8. https://doi.org/10.1038/s41598-017-18259-0.

[46] Jian H, Liu Y, Wang X, Dong X, Zou X. Akkermansia muciniphila as a next-generation probiotic in modulating human metabolic homeostasis and disease progression: a role mediated by gut–liver–brain axes? Int J Mol Sci 2023;24. https://doi.org/10.3390/IJMS24043900.

[47] Zhang YW, Song PR, Wang SC, Liu H, Shi ZM, Su JC. Diets intervene osteoporosis via gut-bone axis. Gut Microb 2024;16. https://doi.org/10.1080/19490976.2023.2295432.

[48] Lyu Z, Hu Y, Guo Y, Liu D. Modulation of bone remodeling by the gut microbiota: a new therapy for osteoporosis. Bone Research 2023;11(1):1–15. https://doi.org/10.1038/s41413-023-00264-x. 2023;11.

[49] Patsch JM, Burghardt AJ, Yap SP, Baum T, Schwartz AV, Joseph GB, et al. Increased cortical porosity in type-2 diabetic postmenopausal women with fragility fractures. J Bone Miner Res 2013;28:313. https://doi.org/10.1002/JBMR.1763.

[50] Roseti L, Desando G, Cavallo C, Petretta M, Grigolo B. Articular cartilage regeneration in osteoarthritis. Cells 2019;8:1305. https://doi.org/10.3390/CELLS8111305. 2019;8:1305.

[51] Upadhyay P, Kalra D, Nilakhe AS, Aggrawal V, Gupta S. Polyherbal formulation PL02 alleviates pain, inflammation, and subchondral bone deterioration in an osteoarthritis rodent model. Front Nutr 2023;10. https://doi.org/10.3389/FNUT.2023.1217051/FULL.

[52] Sewing L, Potasso L, Baumann S, Schenk D, Gazozcu F, Lippuner K, et al. Bone microarchitecture and strength in long-standing type 1 diabetes. J Bone Miner Res 2022;37:837. https://doi.org/10.1002/JBMR.4517.
[53] Gazzotti S, Aparisi Gómez MP, Schileo E, Taddei F, Sangiorgi L, Fusaro M, et al. High-resolution peripheral quantitative computed tomography: research or clinical practice? Br J Radiol 2023;96. https://doi.org/10.1259/BJR.20221016.
[54] Wu Z, Deng W, Ye Y, Xu J, Han D, Zheng Y, et al. Liraglutide, a glucagon-like peptide-1 receptor agonist, inhibits bone loss in an animal model of osteoporosis with or without diabetes. Front Endocrinol 2024;15:1378291. https://doi.org/10.3389/FENDO.2024.1378291/BIBTEX.