Exploring the Interplay between Vitamin D, Insulin Resistance, Obesity and Skeletal Health

Mohammed N. Abed¹, Fawaz A. Alassaf², Mohannad E. Qazzaz³

¹Department of Pharmaceutical Chemistry, College of Pharmacy, University of Mosul, Mosul; ²Department of Pharmacology and Toxicology, College of Pharmacy, University of Mosul, Mosul; ³Department of Pharmacognosy and Medicinal Plants, College of Pharmacy, University of Mosul, Mosul, Iraq

Vitamin D (ViD), plays an important role in calcium absorption and bone mineralization, is associated with bone mineral density. Severe deficiency in ViD has long been linked to conditions such as rickets in children and osteomalacia in adults, revealing its substantial role in skeletal health. Additionally, investigations show an existing interconnection between ViD and insulin resistance (Ins-R), especially in patients with type 2 diabetes mellitus (T2DM). Obesity, in conjunction with Ins-R, may augment the risk of osteoporosis and deterioration of skeletal health. This review aims to examine recent studies on the interplay between ViD, Ins-R, obesity, and their impact on skeletal health, to offer insights into potential therapeutic strategies. Cochrane Library, Google Scholar, and Pubmed were searched to investigate relevant studies until December 2023. Current research demonstrates ViD’s impact on pancreatic β-cell function, systemic inflammation, and insulin action regulation. Our findings highlight an intricate association between ViD, Ins-R, obesity, and skeletal health, providing a perspective for the prevention and/or treatment of skeletal disorders in patients with obesity, Ins-R, and T2DM.

Key Words: Bone and bones · Insulin resistance · Obesity · Vitamin D

INTRODUCTION

Knowledge of the biology and physiology of the human skeletal system has advanced greatly in the last few years. Nonetheless, numerous aspects remain to be thoroughly elucidated or completely understood. Meanwhile, bone health has become an important topic for both clinical and basic researchers.[1] In general, the preservation of bone health relies on the continuous process of normal bone remodeling, a dynamic interplay where bone resorption and formation harmoniously maintain bone microarchitecture, strength, and mineral balance. Multiple internal (hormones, growth factors, and cytokines) and external (nutrients, medications, and environmental toxins) elements intricately impact this orchestrated physiological mechanism. Any disruption in this balance may lead to dysregulated bone remodeling, potentially predisposing individuals to bone loss conditions like osteoporosis.[2] Currently, the treatment of osteoporosis, which is the primary reason for approximately 9 million fractures per year globally, is not completely effective due to various factors. One of these factors is insulin resistance (Ins-R),
where previous studies have revealed a crucial role for insulin in the anabolic potential on a mass of bone and the microarchitecture of trabecular bone, where resistance to this action may augment the risk of fractures.[3-5] Research endeavors have highlighted contrasting patterns regarding bone mineral density (BMD) in diabetes: typically reduced in type 1 diabetes mellitus and either normal or elevated in type 2 diabetes mellitus (T2DM).[6] Resistance to insulin action in T2DM has been shown to predispose patients to a higher risk of fracture mainly due to changes in the structure of bone; such as diminished cortical density and improved cortical porosity.[7] This phenomenon indicates that Ins-R hinders the way by which insulin affects bone mass. Of the major characteristics of Ins-R is obesity, which is another contributor to reduced bone health. On the other hand, obese individuals have augmented resistance to the cellular actions of insulin, which further complicates the problem.[8] The heightened risk associated with obesity and Ins-R has been shown to exert multifaceted effects on bone architecture through diverse mechanisms.[9] These include alterations in body weight, increased fat volume, modulation of bone formation and resorption rates, as well as the influence of proinflammatory cytokines within the bone marrow microenvironment.[10,11] Furthermore, extensive evidence underscores obesity's role in exacerbating and accelerating detrimental impacts on overall health, notably contributing to compromised bone health, with augmented accumulation of adipose tissue, impaired bone structure, and increased susceptibility to bone fragility.[12] Therefore, addressing obesity and managing Ins-R by health care professionals may indirectly impact bone health by improving overall metabolic health, reducing inflammation, and restoring hormonal balance.[13] ViD, as an important therapeutic option for patients with osteoporosis has extensively been studied. The well-established role of ViD has primarily revolved around its impact on skeletal health, affecting mineralization, bone turnover, and fracture susceptibility, thus aiding in osteoporosis prevention and treatment. However, the recent revelation of widespread ViD receptors (VDR) in non-skeletal tissues has significantly heightened interest in this vitamin as a possible therapeutic candidate for preventing chronic diseases.[14] We have previously reported diverse roles for ViD in affecting multiple diseases and hormones, including allergic rhinitis, thyroid hormones, parathyroid hormones, sex hormones, prolactin, adrenal hormones, and vasopressin.[15-20] ViD's involvement in the mechanisms underlying the development of Ins-R and
obesity among diabetic individuals has recently been documented. The vitamin might help to provide better glycemic control through increasing glucose uptake, in addition to stimulating the secretion of insulin.[21] Therefore, this review has aimed to investigate the interplay between ViD, Ins-R, obesity and their impact on skeletal health. Additionally, the role of ViD in modulating the course of these diseases will also be explored. The clinical importance of this investigation may provide insights into potential therapeutic or preventive strategies or preventive to minimize skeletal problems.

INSULIN RESISTANCE AND SKELETAL HEALTH

Ins-R, refers to a condition in which muscle fails to utilize glucose accompanied by more production of glucose from the liver, which results in raised blood sugar levels during fasting and after meals. The resistance to insulin action is regarded as a crucial factor for multiple diseases, including T2DM.[22,23] Bone fragility is one of the complications of T2DM, and Ins-R is expected to contribute to diabetes-related bone deficits. In diabetes mellitus, various intricate mechanisms collectively contribute to the heightened risk of fractures. These encompass hyperglycemia, oxidative stress, and the accumulation of advanced glycation end products (AGE), which adversely affect collagen properties.[24] Additionally, there is an increase in marrow adiposity, the release of inflammatory factors and adipokines from visceral fat, and possible alterations in the function of osteocytes. These factors interrelate, potentially leading to Ins-R-induced osteoporosis among diabetic patients.[25,26] A recent report suggests that an inflammatory environment within the bone may serve as a significant mechanism, triggering unregulated bone resorption and insufficient bone formation, consequently leading to greater bone porosity. Investigations have noted a potential link between elevated blood glucose levels, Ins-R, and heightened activity of CD4+ T-cells within the bone marrow. Consequently, the activation of these CD4+ T-cells within the bone marrow might contribute to diminished bone quality and Ins-R in T2DM.[27]

It is also evident that bone is one of the sites of Ins-R and could contribute to the severity of glucose intolerance and Ins-R in the entire body of individuals with T2DM.[28] Observations of the preclinical and clinical studies highlight intriguing associations between Ins-R and skeletal health. Although some investigations suggest a confirmed correlation between increased Ins-R and greater bone density, adjustments for body size tend to attenuate these relationships.[29] Investigations involving large participant pools indicate a complex interplay between Ins-R, β-cell function, osteoporosis, and BMD, particularly concerning varying levels of Ins-R. In a study involving 5,292 participants, researchers explored the connections between Ins-R, β-cell secretion, osteoporosis, and BMD. They observed that the relationship between β-cell function and BMD/osteoporosis altered with increasing Ins-R levels. At lower levels of homeostasis model assessment of insulin resistance (HOMA-IR) (<2), β-cell function showed a negative association with osteoporosis. However, this association did not remain statistically significant when HOMA-IR was ≥2.[30] A recent cross-sectional study sought to explore the correlation between β-cell function, Ins-R and levels of turnover markers of bone in individuals with abnormal glucose metabolism. The obtained data revealed that lower levels of bone turnover markers were linked to higher rates of Ins-R and compromised function of β-cell in patients with dysglycemia. Therefore, pointing out the changes in bone turnover in patients with diabetes or hyperglycemia may help in predicting the development of osteoporosis and fractures. Moreover, this approach could provide a suitable alleviating measure to reduce patient discomfort and long-term complications.[31] Additionally, investigating the correlation between Ins-R and the risk of osteoporosis in a retrospective analysis that was conducted on 234 T2DM individuals, concluded that augmented levels of Ins-R could be linked to higher risk rates of osteoporosis.[32]

Unlike the documented connection between T2DM and the higher risk of fractures, exploring the link between Ins-R, BMD, and incidence of non-spine fractures in non-diabetic individuals reported that a higher rate of Ins-R leads to elevated BMD. However, upon adjusting for BMD and body mass index (BMI), the study did not show any evidence supporting a link between higher Ins-R and an augmented possibility of fractures.[33] Evolutions in bone imaging techniques now enable the assessment of intricate aspects of bone quality and resilience beyond conventional BMD evaluations. For instance, recent studies have focused on the lumbar spine trabecular bone score, a novel measure adopted from X-ray absorpti-
OBESITY AND SKELETAL HEALTH

Growing evidence suggests a complex connection between body fat and osteoporosis within the realm of obesity, surpassing the simple relationship between body weight and bone density. Despite initial beliefs that obesity might benefit bone health, recent studies contradict this idea, demonstrating that excessive body fat can harm the skeletal system, particularly in post-menopausal women, increasing the risk of fractures.[35,36] The primary molecular mechanisms linked to both obesity and bone reduction include increased oxidative stress, disrupting bone-regulating hormones, Ins-R, interference by non-coding RNA, inflammation (via the production of proinflammatory adipokines and osteokines), altering bone cell functioning and modulating gut microbiota.[37] Bone quality encompasses various aspects like bone remodeling, microarchitecture, and material properties, such as skeletal toughness, strength, and fracture. Concerning BMD, obesity commonly correlates with increased BMD and bone mineral content (BMC), which constitute standard measurements for evaluating the mass of skeletal bone in the investigated people.[38] Studies show a progressive rise in BMD with increasing BMI across different age groups, from young to elderly individuals, encompassing those with normal weight to extremely obese individuals. This positive relationship between BMI and BMD/BMC is observed, particularly in post-menopausal women. However, despite these higher measurements, it seems that the altered quality of bone might be a significant factor influencing fracture risk in this population.[39,40] Besides, it has also indicated that obesity affects bone quality, potentially explaining why obese individuals face a higher fracture risk despite having similar BMD to normal persons; where it has been revealed that obesity is linked to reduced bone turnover, and bone formation seems to decrease more than bone breakdown.[41] Accordingly, exploring different criteria for defining obesity, apart from BMI, is essential to understanding its connection to bone fragility. During examining body composition, a positive link was noted between lean body mass and BMD, while the percentage of body fat might actually show a negative correlation with BMD. Therefore, it's also suggested that although individuals with obesity tend to have higher BMD values, this increase might not be adequate to withstand the larger impact forces experienced during falls or other biomechanical stressors affecting the skeleton.[42] One contributing factor to the elevated bone mass observed in obesity is believed to be increased mechanical load. However, this higher bone density might not fully counteract the impact forces during certain movements or traumatic incidents. The mechanical stress experienced by bones that bear weights like the femur, lumbar spine, and hip, surpasses that on the upper extremities that do not bear weights.[43] Hence, it is crucial to examine specific bone responses to obesity across different areas of the skeleton, particularly due to the above-mentioned mechanical stress on some bones, which are regarded as potential spots for osteoporosis fractures in elderly individuals, mainly women. However, the association of mechanical load with BMD is intricate. Despite this complexity, it has been shown that increased BMD is associated with obesity across all skeletal sites in older individuals.[44] Research indicates that bones of weight-bearing potential are more significantly impacted by obesity compared to others like the radius.[38] Conversely, there is a reported significant direct relationship between BMD and BMI, however with an increased risk of fractures, in distal radius of adolescent and young adult females with obesity.[45]

The impact of obesity duration on changes in bone mass is another concern, however still not fully clear. Typically, most studies lack information regarding the duration of obesity before investigation. Factors like the duration or age when obesity began, such as life-long obesity versus a shorter duration, could potentially induce noted BMD differences. Additionally, it is essential to consider that a longer duration of obesity is often linked to a higher risk of developing related conditions such as T2DM and metabolic syndrome.[38] Furthermore, the presence of conditions like hyperinsulinemia and Ins-R in obesity might diminish the positive impact of pancreatic hormones on bones, contributing partly to the elevated fracture rates observed in obese individuals, especially those with diabetes.[46] Obesity occurring alongside Ins-R and T2DM, conditions already linked to higher fracture risk, disrupted bone microarchitecture (like increased cortical porosity), and changed bone turnover, could potentially worsen bone health in individuals dealing with obesity.[47] Research indicates that weight loss can alter the dangers linked to childhood obesity, yet the degree of risk reduction is influenced by the timing of
weight loss. Typically, shedding excess weight early—prior to puberty tends to be more advantageous, although specific diseases show notable variations in this pattern.[48]

The relationship between fat distribution and its impact on bone strength goes beyond sheer quantity. Where and how fat accumulates in the body plays a crucial role. Visceral fat, located around organs in the abdomen, appears to negatively affect bone structure and strength. Conversely, subcutaneous fat, found just beneath the skin, exhibits more protective associations.[49] This is regarded as a crucial factor for bone health because adipose tissue, acting as a central hub for various hormones and inflammatory elements, regulates numerous bodily functions. This hormonal connection further complicates the association between adipose tissue and bone. Hormones like insulin, leptin, and adiponectin have a dual impact on bone metabolism, making their overall impact uncertain.[50] Differences in gene expression among fat deposits have a significant impact on these functions. For example, protective proteins like adiponectin, crucial in averting osteoporosis, are expressed less in visceral fat compared to subcutaneous fat. Similarly, leptin, a hormone influencing satiety and bone cell formation while reducing bone breakdown, seems less prevalent in visceral fat.[51] Low levels of adiponectin and high visceral adiposity can influence Ins-R and β-cell dysfunction, potentially predisposing individuals to skeletal issues.[52] While estrogen conversion from testosterone via aromatase in adipose cells can potentially prevent bone loss, especially in post-menopausal obese women, the expression of aromatase, responsible for reducing bone-weakening activities, is lower in visceral fat cells. Although estrogen plays a vital role, it’s not the sole hormonal connection between adipose tissue and bone. Additionally, visceral fat is associated with heightened levels of pro-inflammatory cytokines like interleukin (IL)-6 and tumor necrosis factor-α, both contributing to bone breakdown and osteoporosis.[53] The complex interaction of hormone regulation, inflammatory factors, and fat distribution characterizes the link between adipose tissue and bone health. This relationship, which depends on several contributing factors, characterizes how obesity impacts bone metabolism. These include the type and distribution of fatty tissue, age, gender, and particular bone locations, in addition to the mechanical pressure caused by body weight. Additionally, cytokines secreted within the body could also play a significant role in determining bone health.[10]

VITAMIN D, INSULIN RESISTANCE, OBESITY AND OSTEOPOROSIS

ViD, a fat-soluble nutrient, plays a central part in absorbing calcium with mineralizing bones, showing a positive link to BMD. Prolonged and severe deficiencies in ViD are well-known to result in conditions like rickets in children and osteomalacia in adults. The prevalence of insufficient ViD levels in various populations, especially among older individuals, is a worry, underscoring the need for effective approaches to enhance bone health.[54] Remarkably, ViD has been shown to improve insulin sensitivity and regulate blood sugar levels, where its deficiency has been linked to the development and progression of T2DM and possibly with increased occurrence of several diabetic complications. Besides, ViD deficiency is a common feature in individuals with T2DM, leading to higher rates of osteoporosis. The concept of diabetic osteopathy, characterized by reduced bone formation and density leading to increased risks of fractures, underlines the urgent need for predicting and addressing these diabetes-related conditions.[55] Ins-R, a central feature of T2DM, significantly augments their osteoporosis likelihood. It has been reported that low serum ViD level is significantly linked to Ins-R and abnormal bone metabolism in patients with T2DM.[56] Therefore, investigation of serum ViD has drawn attention to understanding the factors that lead to the onset T2DM in addition to treatment plans. Among elderly patients with T2DM, a connection between serum ViD levels, muscle and bone mass, and Ins-R has been identified. In these patients, ViD deficiency aggravated Ins-R and contributed to muscle mass loss and reduced bone density.[57] Moreover, the potential advantages of ViD in improving the function of pancreatic β-cells, reducing Ins-R, and alleviating systemic inflammation have been determined. The direct binding of ViD to pancreatic β-cell VDR and indirect regulation of extracellular calcium flow through these cells point to its significance. These actions of ViD explain its importance for insulin-responsive tissues.[58] Recent comprehensive analyses of randomized controlled trials show that ViD supplementation leads to decreases in fasting plasma glucose, hemoglobin A1c (HbA1c), and HOMA-IR among individuals with T2DM. However, the observed differences within these studies may be due to variations in serum ViD levels, characteristics of supplementation (such as dosage and duration), BMI, and ethnicity.[59,60]
The proposed mechanism underlying the link between ViD, Ins-R, obesity and skeletal health could be related to the role of ViD in the function of the β-cell of pancreas. This is widely confirmed by understanding the activity and distribution of 1 α-hydroxylase enzyme, which is previously known to be only found in kidneys. However, the detection of this enzyme in the pancreatic islet cells and by verifying its ability to convert ViD from the inactive to active form within these cells suggested local formation of calcitriol. The local formation of active ViD helps in improvement of pancreatic β-cell functions to produce more insulin via ViD-dependent insulin production, secretion, and ultimately alleviation of Ins-R.[61] A study performed by Kjalarsdottir and colleagues to reveal the transcriptional functions of VDR in the β-cell functions in mice and human pancreatic islet cells, showed that pre-incubation of the cells with active ViD improved glucose-induced insulin secretion and enhanced glucose-provoked influx of calcium. Therefore, these data indicate the possible enhancement of calcium influx through the voltage-gated calcium channel by ViD, which in turn regulates the function of β-cells to produce insulin.[62] On the other hand, the role of ViD in boosting the sensitivity of cells to insulin via impacting the receptors on its muscle cells may improve obesity and T2DM by increasing insulin secretion and minimizing InsR. This is mainly performed through upregulation of insulin receptors number and sensitivity to insulin, alongside the effect on peroxisome proliferator-activated receptor-γ (PPARγ) and the effect on controlling extracellular calcium.[63] Additionally, the improved insulin secretion and reduced InsR-driven by ViD could offer an essential anabolic potential on the bone mass and microarchitecture. Enhanced bone cells proliferation and induced collagen biosynthesis as a result of insulin administration that was noted during the use of cultured osteoblasts, besides the ability of insulin to produce a synergistic effect with parathyroid hormone and insulin-like growth factor-1, would greatly support the proposed link between ViD, Ins-R, obesity and bone health.[30]

Generally, osteoporosis is frequently viewed as an inflammatory ailment, with pro-inflammatory cytokines linked to heightened bone activity. This scenario is highly noted in obese persons, where obesity triggers persistent body-wide inflammation potentially inducing Ins-R, dysfunction in β-cells, and eventually predispose to T2DM. This ongoing state of inflammation contributes to the extended complications of diabetes, encompassing conditions like osteoporosis.[64,65] Additionally, mild, systemic inflammation is likely detrimental to bone health, and heightened bone marrow adipogenesis might result in reduced BMD among individuals dealing with obesity.[66] Moreover, the link between ViD deficiency and higher BMI levels exists among both diabetic and non-diabetic individuals, featuring the complex connection between obesity, Ins-R, and ViD levels.[67] The widespread occurrence of ViD deficiency in obese individuals is a well-established observation, likely stemming from the dispersion of ViD into larger volumes of fat, serum, liver, and muscle. However, other mechanisms may also contribute simultaneously, although they are not entirely ruled out. Despite this, the idea that low ViD might directly cause obesity remains uncertain, as its effects via VDR in adipose tissue are still not fully explained.[68]

Acknowledging oxidative stress as a causative element in both obesity and Ins-R could additionally affect bone health. Oxidative stress is harmful as the surplus reactive oxygen species (ROS) causes cellular harm, specifically targeting DNA and leading to lipid peroxidation.[69-71] Indeed, variations in ROS and/or antioxidant mechanisms appear to play a role in the development of bone degradation. Oxidative stress disrupts the bone remodeling process, creating an imbalance between the activities of osteoclasts and osteoblasts as shown in Figure 1. This imbalance can contribute to metabolic bone disorders and the progression of skeletal conditions like osteoporosis, characterized by decreased BMD and a reduction in bone mass. ROS triggers the apoptosis of osteoclasts and osteocytes, favoring the formation of osteoclasts while impeding mineralization and osteogenesis. Excessive apoptosis of osteocytes, driven by oxidative stress, creates an imbalance that favors osteoclast formation, leading to increased turnover in bone remodeling and subsequent bone loss.[72] Moreover, there existed a substantial occurrence of ViD deficiency, with 25-hydroxy-ViD levels linked to increased levels of oxidative stress and markers of inflammation.[73] Low ViD levels disrupt mitochondrial functions, leading to increased oxidative stress and systemic inflammation. ViD interacts with its intracellular receptors, influencing ViD-dependent gene expression and activating ViD-responsive elements, initiating multiple second messenger systems. Consequently, the prevalence and severity of various diseases rise due to ViD deficiency, particularly metabolic disorders associated with oxidative stress, such as obesity, Ins-R, T2DM, systemic inflammatory condi-

[https://doi.org/10.11005/jbm.2024.31.2.75](https://doi.org/10.11005/jbm.2024.31.2.75)
Vitamin D’s Impact on Insulin Resistance, Obesity, and Skeletal Health

Insulin resistance, obesity, and low vitamin D level are all common features of type 2 diabetes mellitus. These factors augment oxidative stress by increasing reactive oxygen species (ROS) and reducing the total antioxidant status (TAS) causing apoptosis of osteocytes, inhibition of osteoblasts, and activation of osteoclasts. The antioxidant potential of vitamin D may provide bone protection (Fig. 1).

CLINICAL ASPECTS

Distinguishing the distinct impacts of the duration of disease, metabolic regulation, and the occurrence of complications in T2DM poses challenges due to their strong interconnection within the condition.[77] However, it is indicated that a duration of T2DM exceeding 10 years significantly heightens the risk of fragility fractures, irrespective of diabetes management.[78] Generally, an extended duration of T2DM appears to negatively influence bone metabolism, although it is crucial to note that T2DM often goes undiagnosed for considerable periods. Apart from the length of diabetes, inadequate control of glycemia has shown to be linked to higher rates of fractures in T2DM.[79] A substantial, extended prospective study covering over 4,000 individuals and spanning an average follow-up of 12 years specified that the hazard of fractures was comparable between non-diabetic individuals and those with well-managed T2DM. However, individuals with poorly controlled T2DM showed a 1.6-fold increase in fracture risk. The trial findings align with extensive evidence from observational studies, supporting the notion that ViD plays a role in influencing the risk of fracture in diabetes.[80] Concerning the optimal level of ViD, the guideline stated by the Endocrine Society for Clinical Practice set levels of ViD deficiency, insufficiency, or adequacy as concentrations of ViD of less than 20 ng/mL, between 21 and 29 ng/mL, and between 30 and 100 ng/mL of serum, respectively. Additionally, observational studies reported a link between healthy values...
of serum ViD (range, 40–60 ng/mL) with reduced mortality and risk of progression of numerous chronic diseases. Accordingly, monitoring of serum ViD levels is essential, especially in patients with T2DM, to achieve the desired bone health.[81] In general, the primary approach to managing ViD deficiency involves ViD supplementation aimed at preventing or improving the condition. It has been suggested that ViD supplementation may impact glucose regulation and enhance Ins-R. For instance, ViD supplementation to pre-diabetic rats significantly improved fasting blood glucose, HbA1C, insulin levels and HOMA-IR. Additionally, its supplementation resulted in a decline in degeneration of the islet of Langerhans upon histological analysis. Moreover, Vitamin D altered the IL-6/IL-10 ratio, boosted PPARγ expression, and reduced nuclear factor-κB phosphorylation.[82] Additionally, a clinical investigation into risk factors for Ins-R and the impact of ViD supplementation on glucose and lipid metabolism among patients with T2DM revealed that insufficient ViD levels independently affect Ins-R, and supplementing with ViD can enhance glucose and lipid metabolism in individuals dealing with Ins-R and T2DM.[83]

ViD deficiency in obese individuals does not appear to impact bone tissue but might affect other organs. However, studies have shown inconsistent results, and the benefits of ViD supplementation for the dysmetabolic state are not conclusively established.[68,84] Nevertheless, ViD supplementation remains a viable option for individuals who continue to have insufficient ViD levels following weight loss. Additionally, the immunoregulatory functions of ViD might influence the impact of cytokines on bone health and subsequent fracture risk, offering a potential role in managing osteoporosis among obese individuals.[85,86]

Research has backed the antioxidant attributes of ViD. Most of this molecule’s benefits are associated with its anti-oxidative and anti-inflammatory abilities, either directly or indirectly. It has been shown that ViD significantly impacts the body’s organs in addition to its crucial function in maintaining calcium homeostasis. ViD deficiency has been associated with an increased risk of chronic disease morbidity and mortality.[87] This could be applicable to bone health, where the antioxidant properties could add a beneficial impact on skeletal health through its antioxidant potential, an effect that extends beyond its bone mineralization properties as shown in Figure 1. Optimal ViD levels contribute to reduced oxidative stress, enhancing both mitochondrial and endocrine functions, thereby lowering the risks associated with conditions like autoimmunity, infections, metabolic imbalances, and impaired DNA repair. This collective impact supports a healthier and more graceful aging process. Additionally, ViD serves as a potent antioxidant, fostering balanced mitochondrial activities, and preventing protein oxidation, lipid peroxidation, and DNA damage related to oxidative stress.[88] The mechanisms through which ViD mitigates oxidative stress are still under discussion. ViD might operate through genomic pathways to alleviate oxidative stress. Elevated formation of ROS could prompt hypermethylation in gene promoter regions, potentially impacting genes responsible for combating oxidative stress. By upholding the DNA demethylase expressions, that downregulate hypermethylation in the promoter regions of the gene, ViD might contribute indirectly to minimizing the degree of oxidation to pose an anti-oxidative stress property in tissues affected by Ins-R.[61] Emerging insights into ViD’s impact on metabolomics, transcriptomics, and epigenetics, particularly regarding its capacity to manage oxidative stress alongside micronutrients, vitamins, and antioxidants, after restoring normal ViD levels in both serum and tissues, hold promise for more cost-effective and improved clinical outcomes in individuals dealing with osteoporosis, obesity, Ins-R, and T2DM.

Among other potential clinical aspects influencing the heightened fracture risk in T2DM, which is accompanied by obesity and Ins-R, are the antidiabetic medications. These medications might exert direct impacts on bone cells or an indirect potential on the metabolism of bone, in addition to their effect on ViD levels.[89] Recently, metformin has extensively been investigated as a promising treatment for skeletal disorders, including osteoporosis. Overall findings of the investigations suggest that metformin has either positive or neutral effects on the risk of fractures in T2DM population. Metformin appears to improve BMD, in addition to reduction of the impacts of T2DM on adiposity formation.[90] Additionally, elderly male T2DM patients can effectively regulate their blood glucose levels with both high and low doses of metformin. In individuals with T2DM, however, the advantages of high-dosage metformin were more evident in terms of increasing BMD and bone metabolism. Besides, ViD level was significantly improved in patients group after the administration of metformin.[91]
Sulfonylureas potentially stimulate the differentiation and proliferation of osteoblasts while also providing protection for these cells against the impact of high blood sugar levels. However, a recent cross-sectional study by Zhang and colleagues [92] showed that patients on sulfonylureas had a greater fracture rate than patients in the other group, indicating that sulfonylurea usage considerably raised the risk of fractures in people with diabetes, likely due to the increased possibility of experiencing low blood sugar levels (hypoglycemia) when using them. Moreover, a meta-analysis investigated the fracture risk among patients with T2DM revealed that sulfonylurea use was associated with 14% increase in the risk of developing fracture in T2DM, where this risk was higher than metformin.[93] However, glimepiride, a third-generation sulfonylurea, was shown to induce osteogenic differentiation of osteoblasts in a high glucose microenvironment, where this effect was attributed to peculiar pleiotropic effects of this drug.[94] Concerning ViD supplementation to T2DM patients on different antidiabetic agents, a study showed that ViD did not have an adverse interaction with anti-diabetic agents. Interestingly, the study postulated that supplementing with ViD may be the best way to stop the usual drop in blood high-density lipoprotein levels that occurs when people take sulfonylureas.[95]

In relation to thiazolidinediones (TZDs), these medications function through PPARγ activation and can lead to heightened bone marrow fat and reduced osteoblastogenesis, consequently lowering bone formation. Clinical evidence indicates that in older individuals with T2DM, the use of TZDs correlates with decreased BMD in the hip and the neck of femur, as well as increased fracture risk. Therefore, healthcare providers, not limited to physicians, should diligently assess the presence of osteoporosis risk factors and susceptibility to fractures in patients prior to prescribing TZDs. Additionally, it is strongly advised to maintain regular clinical monitoring of individuals undergoing this treatment.[96] Determination of the effect of ViD supplementation in a cohort study on T2DM population showed that ViD supplementation in the rosiglitazone users increased the mean circulating level of the vitamin and had favorable effects on the circulating triglycerides.[95]

Regarding glucagon-like peptide-1 (GLP-1) receptor agonists, it has been reported that these agents affect bone by supporting its formation, preventing its resorption, and harmonization these actions. Thus, they can enhance the density and quality of bone, in addition to reducing fracture rates in T2DM patients.[97] GLP-1 receptor agonists exerted dramatic anti-osteoporosis potential for those with postmenopausal osteoporosis.[98] However, findings from a recent report have demonstrated a neutral impact of GLP-1 receptor agonists on BMD and the turnover markers and did not affect fracture rates when compared to other hypoglycemic agents.[99]

In the case of dentin phosphophosphatase-4 inhibitors, recent findings might elucidate their favorable impact on BMD and the risk of osteoporosis. Studies in bone biology indicate that these inhibitors enhance markers associated with bone formation, decrease the risk of fractures, and improve both BMD and the quality of bones. These observations suggest a potential contribution to boosting osteoblast activity.[100,101]

Regarding sodium glucose cotransporter 2 (SGLT2) inhibitors, preclinical and clinical data available suggest that these agents might have adverse effects on bone health, but there’s controversy in the data related to fracture risk.[102] Investigating the risk of major osteoporotic fractures with SGLT2 inhibitors revealed no effect on fracture risk when compared to GLP-1 receptor agonists.[103] However, in a recent study of canagliflozin in healthy volunteers, drug-induced endocrine upset, that may mediate the drug’s adverse effect on bone health, was identified. Presently, it remains unclear whether the adverse effects on bone health associated with SGLT-2 inhibitors are related to their mechanisms or specific to individual compounds.[104]

Insulin therapy becomes an added risk factor for falls and fractures, possibly due to an increased incidence of hypoglycemic episodes in treated patients. In a recent extensive study of type 2 diabetes patients, insulin-only therapy was notably linked to a 1.6-fold higher fracture risk compared to metformin-only treatment. Nevertheless, recent evidence indicates that the use of longer-acting insulins, which pose a lower risk of hypoglycemia, is associated with reduced fracture risk compared to other insulin types. This suggests that the heightened fracture risk linked to insulin use might be partly attributed to a greater likelihood of falls caused by hypoglycemia. However, T2DM people treated with insulin often have a longer period of disease accompanied by numerous complications, this issue may, in some cases, negatively influence bone health and predispose individuals to higher rates of fracture irrespective of insulin effect.

Overall, controlled blood sugar is essential for reducing
the incidence of fracture in those with type 1 and T2DM. A raised fracture risk value was notable in 8% of diabetics, following a meta-analysis, per 1% increase in HbA1c value. [105] Additionally, HbA1c levels over 9% for more than two years in T2DM patients related with a 29% augmentation in the risk of fracture. [106] Moreover, it was revealed that the longer the duration of T2DM, the more elevated the incidence of fracture. Accordingly, it is recommended that clinicians consider the potential negative impact of several antidiabetics on bone health, especially when choosing these agents to treat high blood glucose concentrations in patients with T2DM. Selecting drugs with a verified safety profile is advised, mainly for individuals with poor bone quality or those at increased risk of fractures. [107] However, there is some evidence that contradicts the existing knowledge, where extensive glycemic control that results in hypoglycemia, particularly in elderly groups with long-lasting diabetes, was reported to be associated with higher risk rates of fractures. This was clear in type 2 diabetic Taiwanese populations, especially when HbA1c reduced to less than 7%. [108] Similarly, elderly outpatients with T2DM independently practiced higher rates of fall-related fractures due to hypoglycaemic events. The suggested reasons for such an association may include medication effects, instability during the hypoglycemic episodes, or gait abnormalities, in addition to other traditional risk factors for primary and secondary osteoporosis. [109]

The importance of glucose for the molecular activity of osteoblast, besides understanding the impact of hyperglycemia on bone condition through the lifecycle, comprising the related factors of microvascular damage and inflammation, needs to be fully elucidated and planned as areas of particular concern in future trials. This is crucially important, as peak skeletal mass attainment and consequent bone fragility are thought to be resulted from accumulation of AGE, cortical bone micro-pores, and inhibition of insulin pathway. On the other hand, the greater attention that is required to be exercised when managing elderly individuals with T2DM, due to the hypoglycemic potential of some agents in this patients group, proposes a direction for future studies, especially focusing on the relationship between the incidence of fall-related fractures and hypoglycemia.

CONCLUSION

Investigating ViD’s complex relationships with obesity, bone health, and Ins-R, exposes its potential importance to combat the pathophysiology of these diseases. The clear correlations highlight the necessity of specialized treatments and more studies to clarify mechanisms and improve therapeutic approaches. Comprehending these interactions opens up the possibility of customized strategies for improving skeletal health, controlling Ins-R, and addressing issues linked to obesity. Furthermore, the available data suggests that ViD supplementation may have a role in combination with conventional therapy for T2DM patients, to enhance insulin, HbA1c, and Ins-R.

DECLARATIONS

Acknowledgments
We acknowledge the guidance and assistance provided by the University of Mosul and the College of Pharmacy.

Ethics approval and consent to participate
Not applicable.

Conflict of interest
No potential conflict of interest relevant to this article was reported.

ORCID
Mohammed N. Abed
https://orcid.org/0000-0002-2253-4420
Fawaz A. Alassaf
https://orcid.org/0000-0002-2933-9185
Mohannad E. Qazzaz
https://orcid.org/0000-0001-7816-5321

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