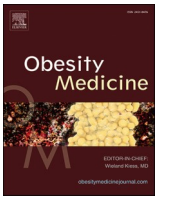
Obesity Medicine 59 (2026) 100680

Contents lists available at ScienceDirect

Obesity Medicine

journal homepage: www.elsevier.com/locate/obmed



Vitamin D deficiency in obesity: Epidemiological evidence, biological mechanisms, and clinical considerations

Reem J. Al Argan [a,*], Safi G. Alqatari [a], Abrar J. Alwaheed [a], Manal A. Hasan [a], Shaya Y. AlQahtani [b], Mohammed D. Al Shubbar [a], Abdullah H. Alnasser [a], Safia M. Al Abbas [a], Noor H. AlYousef [a]

[a] Department of Internal Medicine, College of Medicine, Imam Abdulrahman Bin Faisal University, King Fahad Hospital of the University, Dammam, Eastern Province, Saudi Arabia
[b] Department of Internal Medicine, Critical Care Medicine, College of Medicine, Imam Abdulrahman Bin Faisal University, King Fahad Hospital of the University, Dammam, Eastern Province, Saudi Arabia

ARTICLE INFO

Keywords:
Obesity
Vitamin D
25-Hydroxyvitamin D
Vitamin D deficiency
Adiposity
Metabolism
Supplementation

ABSTRACT

Background: Obesity is a global public health crisis, contributing to substantial morbidity and mortality due to its strong association with chronic diseases such as type 2 diabetes, cardiovascular disorders, and malignancies. Concurrently, vitamin D deficiency has become widespread, affecting nearly one billion people worldwide. Epidemiological studies consistently demonstrate an inverse relationship between obesity and vitamin D levels, with emerging hypotheses suggesting a bidirectional link.

Objectives: This review examines the association between obesity and vitamin D status, the underlying biological mechanisms, the role of vitamin D in metabolic disease, and the implications of vitamin D supplementation in obese populations.

Results: Epidemiological studies confirm that obese individuals exhibit significantly lower circulating 25-hydroxyvitamin D [25(OH)D] levels than their normal-weight counterparts. Mendelian randomization analyses further establish a causal link, indicating that obesity leads to vitamin D deficiency, rather than vice versa. Proposed biological mechanisms include volumetric dilution due to increased adipose tissue, sequestration of vitamin D in fat stores, and obesity-related impairments in vitamin D metabolism. Vitamin D plays a crucial role in metabolic health by influencing insulin secretion, lipid metabolism, and blood pressure regulation. Deficiency has been associated with insulin resistance, dyslipidemia, and overactivation of the renin-angiotensin-aldosterone system (RAAS), exacerbating obesity-related metabolic complications. However, while vitamin D supplementation effectively raises serum 25(OH)D levels, its impact on improving metabolic outcomes remains inconsistent across interventional studies. In addition, the joint impact of obesity and vitamin D deficiency on bone health remains unexplored, despite distinct mechanisms suggesting additive or synergistic harm. Targeted studies are needed to assess their combined effects using robust designs and comprehensive skeletal outcomes.

* Corresponding author. Department of Internal Medicine, College of Medicine, Imam Abdulrahman Bin Faisal University, King Fahad Hospital of the University, Dammam, 31441, Eastern Province, Saudi Arabia.

E-mail addresses: rjalarqan@iau.edu.sa (R.J. Al Argan), sagqatari@iau.edu.sa (S.G. Alqatari), ajwaheed@iau.edu.sa (A.J. Alwaheed), mahasan@iau.edu.sa (M.A. Hasan), saalqahthani@iau.edu.sa (S.Y. AlQahtani), mdshubbar0@gmail.com (M.D. Al Shubbar), abdullah_alnasir@hotmail.com (A.H. Alnasser), s.alabbas013@gmail.com (S.M. Al Abbas), nooraly76@gmail.com (N.H. AlYousef).

https://doi.org/10.1016/j.obmed.2025.100680
Received 11 June 2025; Received in revised form 8 August 2025; Accepted 25 December 2025
Available online 26 December 2025

Conclusions: The strong inverse relationship between obesity and vitamin D status highlights the need for targeted interventions. While weight loss modestly improves vitamin D levels, BMI-adjusted vitamin D supplementation may be the most effective strategy for correcting deficiency in obese populations. Current guidelines suggest that obese individuals require higher doses of vitamin D to achieve optimal serum levels. However, further research is necessary to refine dosing strategies and determine the long-term impact of supplementation on metabolic health outcomes. Future investigations should integrate personalized supplementation approaches with lifestyle and pharmacological interventions to mitigate obesity-related metabolic disturbances effectively. Furthermore, obesity and vitamin D deficiency may jointly exacerbate skeletal deterioration, warranting dedicated investigation.

1. Introduction

Obesity has emerged as one of the most pressing public health challenges worldwide, reaching epidemic proportions and placing immense strain on global healthcare systems. The World Health Organization reported that, as of 2016, more than 1.9 billion adults were classified as overweight, with approximately 650 million individuals meeting criteria for obesity. This alarming prevalence is associated with substantial morbidity and mortality, contributing to approximately 2.8 million deaths each year globally, thereby highlighting an urgent need for effective preventive and therapeutic strategies (Obesity, 2021). Excessive adiposity significantly elevates the risk of numerous chronic diseases, including type 2 diabetes mellitus, cardiovascular disorders, and various malignancies (Vranić et al., 2019). The complex etiology of obesity involves intricate interactions among genetic predisposition, lifestyle behaviors, decreased physical activity, and increased consumption of calorie-dense diets, all of which exacerbate the severity and persistence of this global health crisis (Masood and Moorthy, 2023).

Vitamin D, a fat-soluble secosteroid hormone, has gained considerable recognition for its extensive physiological roles, mediated through vitamin D receptors (VDR) that are ubiquitously expressed across numerous human tissues. Endogenously synthesized in the skin following ultraviolet-B (UVB) radiation exposure, vitamin D can also be obtained exogenously from dietary sources or nutritional supplements. Upon entering circulation, vitamin D undergoes hepatic hydroxylation into its major circulating metabolite, 25-hydroxyvitamin D [25(OH)D], and is subsequently activated in the kidneys to the biologically potent hormone 1,25-dihydroxyvitamin D [1,25(OH)_2D] (Shantavasinkul and Nimitphong, 2022). Classically recognized for its pivotal role in calcium and phosphate homeostasis (Bennour et al., 2022), vitamin D promotes intestinal calcium absorption and ensures adequate mineralization of the skeleton, with severe deficiencies well-documented to cause rickets in pediatric populations and osteomalacia among adults (Vranić et al., 2019). Nevertheless, emerging evidence highlights the extensive extra-musculoskeletal effects of vitamin D, notably its involvement in insulin secretion, immune modulation, cell differentiation and proliferation, as well as muscular function. Consequently, vitamin D is increasingly acknowledged as a pleiotropic hormone with broad implications for overall human health (Vranić et al., 2019).

In recent years, significant scientific attention has focused on elucidating the complex association between obesity and vitamin D status (Karampela et al., 2021). Epidemiological data consistently indicate lower circulating 25(OH)D concentrations among individuals with obesity relative to their normal-weight counterparts (Vanlint, 2013) This relationship is particularly salient considering the concurrent escalation in obesity prevalence and widespread occurrence of vitamin D insufficiency, which currently affects an estimated one billion individuals globally (Palacios and Gonzalez, 2014).

Emerging hypotheses propose a potential bidirectional relationship wherein obesity contributes to decreased vitamin D bioavailability, while vitamin D insufficiency may reciprocally exacerbate obesity-related metabolic dysregulation. Given these compelling epidemiological trends and plausible pathophysiological mechanisms, it is imperative to thoroughly explore the interplay between obesity and vitamin D to enhance clinical understanding and public health outcomes. This review aims to synthesize existing epidemiological evidence, delineate plausible biological pathways, and critically evaluate clinical implications associated with vitamin D status in obese populations. Additionally, it examines the efficacy and impact of vitamin D supplementation strategies in addressing insufficiency among individuals affected by obesity. Ultimately, by clarifying established knowledge, identifying unresolved controversies, and highlighting critical knowledge gaps, this review seeks to advance scientific discourse and inform future clinical and public health initiatives addressing the obesity–vitamin D nexus.

2. Epidemiological evidence

The link between obesity and vitamin D deficiency is a well-established finding in epidemiological research (Mai et al., 2012; Karatas, 2013), with compelling evidence from multiple meta-analyses. A landmark 2015 systematic review and meta-analysis by *Pereira-Santos* et al. synthesized data from 23 observational studies, revealing that obese individuals had a significantly higher prevalence of vitamin D deficiency compared to those with normal body weight (prevalence ratio [PR]: 1.35; 95 % CI: 1.21–1.50) (Pereira-Santos et al., 2015). Furthermore, the risk of deficiency escalated with increasing adiposity, as obesity was associated with a 24 % greater prevalence of vitamin D deficiency compared to overweight individuals (PR: 1.24; 95 % CI: 1.14–1.34). The subgroup analyses further reinforced the strength and consistency of this association across different age groups. Up to 37 % of obese children and adolescents were identified as vitamin D deficient (PR: 1.37; 95 % CI: 1.20–1.56), whereas the prevalence among obese adults and

elderly individuals was 33 % (PR: 1.33; 95 % CI: 1.15–1.54). Notably, further analysis confirmed that this relationship persisted across diverse populations, irrespective of latitude, Human Development Index (HDI), or the serum 25(OH)D threshold used to define deficiency. Notably, studies that used a higher cutoff to define vitamin D deficiency (≤50 nmol/L) observed a stronger association between obesity and deficiency (PR: 1.44; 95 % CI: 1.24–1.68). Despite some heterogeneity across studies, meta-regression analyses indicated that neither age, geographic latitude, HDI, nor sample size significantly influenced the observed effect sizes. This suggests that the association between obesity and vitamin D deficiency is a consistent and globally relevant phenomenon, warranting further clinical attention and public health interventions (Pereira-Santos et al., 2015).

In another landmark study having a pooled sample size of nearly 42000 participants, the observational data demonstrated a clear correlation between body mass index (BMI) and circulating vitamin D levels, with each 1 kg/m^2 increase in BMI being associated with a 1.15 % decrease in 25-hydroxyvitamin D (25[OH]D) concentrations (Vimaleswaran et al., 2013). This robust inverse relationship highlights the strong link between obesity and lower vitamin D status. However, the observational nature of these studies precludes definitive conclusions about causality, and correlation does not imply causation, which necessitated a genetic approach to determine directionality.

Using Mendelian randomization (MR), the study provided compelling genetic evidence that obesity causally leads to reduced vitamin D levels. The BMI genetic risk score, composed of 12 obesity-associated single nucleotide polymorphisms (SNPs), was significantly linked to lower circulating vitamin D, confirming a causal effect of higher BMI on reduced 25(OH)D levels. In contrast, genetic predisposition to lower vitamin D levels (via SNPs affecting vitamin D synthesis and metabolism) showed no association with BMI, even in large datasets, ruling out the reverse causal hypothesis. This evidence strongly supports a unidirectional causal relationship, where obesity causes vitamin D deficiency, but vitamin D deficiency does not lead to obesity (Vimaleswaran et al., 2013).

In summary, A significant inverse relationship between vitamin D deficiency and obesity has been well-established through observational studies across diverse populations (Pereira-Santos et al., 2015). However, while such findings consistently highlight an association, they do not delineate the direction of causality. Genetic studies employing Mendelian randomization have provided greater clarity in this regard, supporting a unidirectional relationship wherein increased adiposity leads to reduced circulating vitamin D levels. In contrast, there is insufficient genetic evidence to suggest that low vitamin D status contributes causally to the development of obesity (Vimaleswaran et al., 2013). This asymmetry is further reflected in interventional studies, which have yielded inconsistent findings. While some randomized trials suggest that vitamin D supplementation may result in reductions in body weight or fat mass (Lotfi-Dizaji et al., 2019), others report no significant benefit (Sneve et al., 2008; Kirsty Forsythe et al., 2012). Importantly, many of these studies are limited by small sample sizes, heterogeneous populations, and methodological variability.

As summarized in Table 1, multiple epidemiological studies have consistently demonstrated an inverse association between serum vitamin D levels and obesity, with higher adiposity linked to lower circulating 25(OH)D concentrations across diverse populations and study designs.

3. Causes of vitamin D deficiency in obesity

Although substantial progress has been made in identifying plausible mechanisms underlying vitamin D deficiency in obesity (Table 2), key challenges remain in establishing their relative contribution, physiological reversibility, and clinical relevance. This section critically examines the current mechanistic hypotheses—volumetric dilution, adipose sequestration, and altered metabolism—highlighting where scientific consensus exists and where further research is needed.

Table 1
Summary of key epidemiological findings.

Study	Study Type	Sample Size	Key Findings	Conclusion
Pereira-Santos et al. (Pereira-Santos et al., 2015)	Meta-analysis of 23 studies		Obese individuals had 35 % higher risk of vitamin D deficiency. Strongest association seen in children/adolescents.	Obesity is consistently linked to lower vitamin D levels across diverse populations.
Vimaleswaran et al. (Vimaleswaran et al., 2013)	Mendelian Randomization	~42,000	Each 1 kg/m^2 BMI increase → 1.15 % reduction in 25(OH)D. Genetic evidence supports causal relationship.	Obesity causes vitamin D deficiency, but deficiency does not cause obesity.
Zhang et al. (Zhang et al., 2016)	Cross-sectional study	1277	Serum 25(OH)D levels were inversely associated with waist circumference, waist/hip ratio, and body fat distribution.	Abdominal obesity, rather than general obesity, is a stronger predictor of lower vitamin D levels in Chinese adults.
Plesner et al. (Plesner et al., 2018)	Cross-sectional study	1484 with overweight or obesity/2143 normal weight controls	16.5 % of obese children and adolescents had vitamin D deficiency (<30 nmol/L), compared to 4.8 % of normal-weight peers.	Vitamin D deficiency is common in obese Danish children and adolescents. The degree of obesity is independently associated with lower serum 25(OH)D levels.
Hajhashemy et al. (Hajhashemy et al., 2021)	Systematic review & meta-analysis of 41 studies	257,699	Obese individuals had significantly lower serum vitamin D levels compared to non-obese individuals. The lowest vitamin D levels were found in those with abdominal obesity, and a dose-response relationship was observed.	Obesity, particularly abdominal obesity, is strongly associated with lower vitamin D levels

Table 2
Summary of key mechanisms proposed to explain the link between obesity and vitamin D deficiency, including current understanding and remaining knowledge gaps.

Mechanism	Description	Supporting Evidence	Unresolved Questions
Volumetric Dilution	An increase in fat, muscle, and organ mass expands the volume of distribution, lowering serum Vitamin D (Vranić et al., 2019)	Pharmacokinetic studies show blunted response to supplementation in obese vs. lean individuals (Drincic et al., 2013; Gallagher et al., 2013; Bolland et al., 2007)	Is this the *primary* mechanism, or do others contribute equally?
Sequestration in Adipose Tissue	Vitamin D accumulates in adipose tissue, where it may become biologically inactive or slowly released, reducing its availability in circulation (Wortsman et al., 2000).	*Wortsman*et al. showed that obese individuals had lower increases in serum 25(OH)D after UVB exposure, suggesting vitamin D is sequestered in fat stores (Wortsman et al., 2000). Radiolabeled studies in rats confirmed that vitamin D rapidly deposits in adipose tissue and is released slowly over time, even during deficiency (Rosenstreich et al., 1971).	Is the sequestered vitamin D physiologically accessible? Does weight loss mobilize stored vitamin D reliably and in clinically meaningful amounts?
Impaired Hepatic 25-Hydroxylation	Obesity may be associated with downregulation of CYP2R1, the hepatic enzyme responsible for converting vitamin D into 25(OH)D, reducing bioactivation.	*Alzohily*et al. observed higher circulating levels of vitamin D3 with disproportionately low levels of 25(OH)D3 in obese individuals. They hypothesized that reduced conversion efficiency — possibly due to CYP2R1 downregulation — contributes to deficiency (Alzohily et al., 2024).	To what degree does impaired hepatic hydroxylation contribute to vitamin D deficiency in individuals with obesity, and can this be reversed through weight loss or metabolic improvement?
Lifestyle and Behavioral Factors	Reduced sun exposure, poor diet, and cultural clothing habits limit intake and synthesis	Supported by epidemiological studies and cross-sectional data (Vranić et al., 2019; Palacios and Gonzalez, 2014)	How much do these factors contribute compared to biological ones?

3.1. Volumetric dilution: established mechanism with unresolved impact

One of the most widely supported explanations for the lower serum 25-hydroxyvitamin D (25[OH]D) levels observed in individuals with obesity is the volumetric dilution hypothesis. This hypothesis posits that obese individuals have a greater volume of distribution for vitamin D due to an increased body mass, particularly in adipose tissue, muscle, and liver, leading to a dilutional effect that reduces the concentration of circulating vitamin D (Vranić et al., 2019) Although total body vitamin D stores may be similar—or even higher—in obese individuals compared to their lean counterparts, the expanded distribution space results in a lower serum 25(OH)D concentration (Carrelli et al., 2017; Mutt et al., 2014; Cominacini et al., 2023). In other words, while the absolute quantity of vitamin D in an obese individual may be comparable to that of a lean individual, it is dispersed across a substantially larger volume of body compartments, including adipose tissue, skeletal muscle, hepatic stores, and serum.

Compelling evidence supporting the volumetric dilution hypothesis is derived from pharmacokinetic analyses and clinical observations. *Bolland* et al. demonstrated that following seasonal sun exposure, obese individuals exhibit a smaller increase in serum 25 (OH)D concentrations compared to lean individuals, likely due to the distribution of newly synthesized vitamin D into their expanded fat and lean mass compartments rather than a direct rise in circulating levels (Bolland et al., 2007). Similar findings have been observed in interventional studies assessing vitamin D supplementation. For instance, when equivalent doses of vitamin D are administered orally, obese individuals consistently display a blunted increase in serum 25(OH)D compared to normal-weight controls, further reinforcing the role of volumetric dilution as a key determinant of vitamin D status in obesity (Gallagher et al., 2013).

A systematic analysis of 23 human trials revealed that in 18 studies, weight loss—particularly reductions in adipose tissue—was associated with an increase in serum 25(OH)D levels. Meta-regression analyses demonstrated a near-significant correlation between weight reduction and rising 25(OH)D concentrations, estimating an increase of approximately 6.0 nmol/L per 10 kg of weight loss. This finding supports the premise that the expanded volume of distribution in obesity plays a pivotal role in lowering circulating vitamin D levels. Additionally, the effect of fat mass reduction on serum 25(OH)D concentrations approached statistical significance, further corroborating the hypothesis that adipose tissue expansion contributes to this dilutional effect. However, the observed increase in 25(OH)D following weight loss was notably smaller than predicted if volumetric dilution were the sole mechanism driving vitamin D insufficiency in obesity. This discrepancy suggests the involvement of alternative mechanisms, such as the sequestration of vitamin D within adipose tissue. The hypothesis that vitamin D is retained within fat stores and is not readily bioavailable further complicates the understanding of its metabolism in obesity. Thus, while volumetric dilution remains a predominant factor, additional pathways may contribute to the dysregulation of vitamin D homeostasis in individuals with obesity (Pannu et al., 2016).

3.2. Sequestration in adipose tissue and possible therapeutic considerations

Closely related to the volumetric dilution hypothesis is the concept of vitamin D sequestration in adipose tissue. As a fat-soluble compound, vitamin D readily accumulates in adipose depots, where it can become trapped, thereby limiting its bioavailability and release into circulation. This phenomenon was first demonstrated by *Wortsman* et al. , who provided early evidence that vitamin D sequestration in adipose tissue may contribute to lower circulating levels in individuals with obesity (Wortsman et al., 2000). Experimental studies further support the rapid uptake and prolonged storage of vitamin D within fat tissue. Classic radiotracer experiments in rodents have shown that after administration of labeled vitamin D_3, the dose was rapidly deposited in adipose tissue. Moreover, this stored vitamin D had a slow and gradual release overtime. When dietary vitamin D intake was subsequently restricted, essential tissues such as the liver and kidneys experienced a marked depletion of their vitamin D reserves, whereas adipose tissue retained a substantial portion of the vitamin D for an extended duration (Rosenstreich et al., 1971) This persistence suggests that once vitamin D enters fat stores, it remains largely sequestered unless mobilized by prolonged deficiency or active lipolysis.

A critical question is whether this sequestered vitamin D can be effectively mobilized during weight loss. If adipose tissue serves as a substantial reservoir of vitamin D, reductions in fat mass might theoretically result in its release back into circulation. However, studies investigating the effects of weight loss on serum vitamin D levels have yielded conflicting results. While some studies report no significant changes in circulating 25(OH)D concentrations following weight loss, others have observed notable increases, particularly in cases of substantial fat mass reduction (Pannu et al., 2016; Mallard et al., 2016; Mason et al., 2011; Coupaye et al., 2013; Tzotzas et al., 2010; Perticone et al., 2019; Himbert et al., 2017). These discrepancies may suggest a potential threshold effect, where only significant reductions in adiposity release enough vitamin D to measurably impact blood levels, with the extent of mobilization influenced by factors such as the magnitude and rate of fat loss, as well as individual variations in vitamin D metabolism.

In summary, adipose sequestration explains why obese individuals have a large depot of vitamin D that is not readily available to the circulation. It is a fundamental part of the volumetric dilution effect—essentially the mechanism by which dilution occurs. From a therapeutic perspective, this means that strategies such as aggressive weight loss have only a limited short-term impact on correcting vitamin D deficiency. A more direct and effective approach is to saturate fat stores by administering higher doses of vitamin D, ensuring that both tissue compartments and circulating levels reach sufficiency. Over time, equilibrium is established where vitamin D input equals output; however, due to the increased storage capacity in obesity, the equilibrium requirement is significantly higher than in individuals with normal body weight.

Since weight loss provides only a modest and transient increase in circulating vitamin D, supplementation must be optimized to counteract volumetric dilution and sequestration. This requires tailored dosing strategies that consider body size, fat mass, and metabolic differences. Standard recommendations, adequate for the general population, may fail to restore vitamin D levels in some obese patients, due to its reduced bioavailability from sequestration and dilution (Bennour et al., 2022). Consequently, vitamin D replacement therapy should be adjusted based on body size to achieve optimal serum concentrations. Consequently, adjustments to

vitamin D replacement therapy based on body size are recommended to achieve optimal serum concentrations.

Drincic et al. demonstrated that obese individuals require higher doses of vitamin D to achieve the same serum 25(OH)D increments as normal-weight individuals. Their findings support weight-based dosing and show that the dose-response in obese subjects was approximately 30 % lower than in non-obese individuals from their prior cohort (Drincic et al., 2013). Furthermore, other studies also suggest that a BMI-based dosing approach may be more effective than fixed-dose regimens. A study conducted in 2021 found that an arbitrary formula of 125 IU/kg/day resulted in better normalization of vitamin D levels and improved musculoskeletal health in individuals with obesity (Sadat-Ali et al., 2021). However, further research is needed to refine these dosing strategies, ensuring long-term efficacy and safety while minimizing the risk of excessive e supplementation.

In summary, significant progress has been made in characterizing adipose tissue as a metabolically inert reservoir of vitamin D, supported by radiolabeling studies and clinical data on blunted responses to supplementation in obesity. However, major questions remain regarding the physiological accessibility of this depot, the threshold of weight loss required to release bioavailable vitamin D, and the variability of these effects among individuals. These uncertainties limit the ability to predict vitamin D status changes during weight reduction. Moving forward, research should focus on quantifying sequestration dynamics through controlled kinetic studies and validating personalized dosing strategies that account for adiposity-driven storage effects.

3.3. Bariatric surgery and vitamin D status

While bariatric surgery may initially appear to improve vitamin D status by reducing adipose tissue mass—and thus diminishing both volumetric dilution and adipose sequestration of the vitamin—it paradoxically contributes to further disturbances in vitamin D metabolism. This is particularly evident following malabsorptive procedures such as Roux-en-Y gastric bypass (RYGB) and biliopancreatic diversion (BPD) with duodenal switch. These surgeries bypass key absorption sites in the duodenum and proximal jejunum and delay the interaction of nutrients with bile acids and pancreatic enzymes, thereby impairing the absorption of fat-soluble vitamins, including vitamin D (Lespessailles and Toumi, 2017). Postoperative vitamin D deficiency is common and increases with time after RYGB; a meta-analysis reported a prevalence of approximately 35 % at 1 year and over 50 % by 5 years postoperatively. Inadequate vitamin D supplementation was associated with a higher risk of persistent deficiency (Gao et al., 2023). Clinical practice guidelines, such as those from the AACE/TOS/ASMBS and the Endocrine Society, recommend high-dose vitamin D supplementation following bariatric surgery—typically at least 3000 IU/day, with higher doses (e.g., 50,000 IU 1–3 times weekly) indicated in cases of severe deficiency or malabsorption—to maintain serum 25(OH)D levels above 30 ng/mL (Chakhtoura et al., 2016).

3.4. Altered vitamin D metabolism

The hepatic hydroxylation of vitamin D_2 and D_3 into 25-hydroxyvitamin D [25(OH)D], the main circulating form, typically occurs efficiently in healthy individuals. This reaction is catalyzed by the microsomal enzyme CYP2R1, which has been definitively identified as the principal 25-hydroxylase responsible for this step in humans (Cheng et al., 2004). While CYP2R1's physiological role is well established, its regulation in obesity remains an area of active investigation. Emerging evidence suggests that hepatic CYP2R1 expression may be downregulated in individuals with obesity, potentially due to hepatic steatosis, systemic inflammation, or broader alterations in liver metabolism commonly observed in this population. This impaired enzymatic conversion may contribute to the characteristic biochemical pattern of disproportionately elevated vitamin D_3 levels relative to 25(OH)D, consistent with a bottleneck in hepatic 25-hydroxylation (Alzohily et al., 2024).

These considerations highlight the importance of recognizing altered vitamin D metabolism as a potential contributor alongside volumetric dilution and adipose sequestration. However, to determine its clinical significance, future research should aim to clarify the extent to which CYP2R1 dysregulation contributes to vitamin D deficiency in obesity, and whether this impairment is reversible through weight loss or metabolic improvement.

3.5. Behavioral and lifestyle factors

Other possible mechanisms contributing to lower 25-hydroxyvitamin D [25(OH)D] levels in obese individuals include reduced sunlight exposure. This may be attributed to differences in clothing habits, and decreased participation in outdoor activities compared to individuals with normal weight. Additionally, dietary factors may play a role, as obesity is often associated with poor nutritional habits, which can contribute to inadequate vitamin D intake. These lifestyle-related factors, alongside the inflammatory and metabolic mechanisms, may further explain the observed vitamin D deficiency in obesity (Vranić et al., 2019; Vanlint, 2013).

4. Metabolic and clinical consequences of vitamin D deficiency in obesity

Vitamin D, long recognized for its essential role in calcium homeostasis and bone metabolism, has gained significant attention for its regulatory influence on multiple metabolic processes, including insulin secretion, insulin sensitivity, lipid metabolism, inflammation, and cardiovascular health (Melguizo-Rodríguez et al., 2021). This broad spectrum of effects is facilitated by the widespread expression of vitamin D receptors (VDR) in key metabolic tissues such as pancreatic β-cells, adipose tissue, skeletal muscle, endothelium, and immune cells, underscoring its critical role in metabolic regulation (Melguizo-Rodríguez et al., 2021; Szymczak-Pajor and Śliwińska, 2019).

4.1. Insulin resistance and type 2 diabetes mellitus

The relationship between vitamin D deficiency and metabolic dysfunction—particularly insulin resistance and type 2 diabetes mellitus (T2DM)—has garnered considerable research interest. While obesity is an established risk factor for insulin resistance, accumulating evidence suggests that vitamin D deficiency may act as an independent or synergistic contributor (Kabadi et al., 2012).

Although observational studies have frequently reported an association between low serum 25-hydroxyvitamin D levels and increased insulin resistance—particularly among individuals with obesity—the evidence remains inconsistent. Some studies propose that vitamin D deficiency acts synergistically with obesity to exacerbate insulin resistance (Kabadi et al., 2012), while others suggest that it may serve as an independent contributor to impaired glucose metabolism (Buyukinan et al., 2012; Delvin et al., 2010). Conversely, certain analyses have challenged the role of vitamin D altogether, reporting no significant association with insulin resistance after adjusting for potential confounding factors (Torun et al., 2013). This heterogeneity across studies underscores the need for better-designed longitudinal and mechanistic investigations to determine whether vitamin D deficiency is causative, contributory, or merely correlative in insulin resistance.

Although the precise mechanisms underlying this potential relationship remain to be fully elucidated, available evidence supports several biologically plausible pathways through which vitamin D may influence glucose homeostasis, including effects on insulin secretion, sensitivity, and inflammation (Szymczak-Pajor and Śliwińska, 2019; Peterson et al., 2014).

Several mechanistic pathways may underlie the proposed link between vitamin D deficiency and impaired glucose homeostasis. One primary mechanism is its role in maintaining pancreatic β-cell function and insulin secretion. Vitamin D directly binds to vitamin D receptors (VDR) within β-cells, promoting insulin gene transcription via genomic pathways. It also exerts non-genomic effects, such as regulating intracellular calcium levels, which are essential for insulin exocytosis (Szymczak-Pajor and Śliwińska, 2019). In peripheral tissues, vitamin D enhances insulin sensitivity by stimulating insulin receptor (IR) gene expression through interactions between VDR–retinoid X receptor (RXR) complexes and vitamin D response elements (VDRE), thereby strengthening insulin signaling and promoting glucose uptake in muscle, liver, and adipose tissue (Szymczak-Pajor and Śliwińska, 2019; Argano et al., 2023).

In addition, chronic low-grade inflammation is a central driver of insulin resistance and metabolic syndrome, and vitamin D exerts notable anti-inflammatory effects. It suppresses the production of pro-inflammatory cytokines, including interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), while enhancing anti-inflammatory mediators (Fuentes-Barría et al., 2025). Deficiency in vitamin D has been associated with elevated levels of these pro-inflammatory cytokines, particularly in individuals with higher BMI, thereby aggravating insulin resistance and metabolic dysfunction (Fuentes-Barría et al., 2025), Conversely, vitamin D supplementation has been associated with reductions in inflammatory markers such as C-reactive protein and TNF-α (Moslemi et al., 2022). Additionally, recent studies suggest that polymorphisms in the vitamin D receptor (VDR) gene may influence the risk of T2DM by affecting VDR expression, posttranslational modifications, and vitamin D binding capacity, thereby impacting insulin secretion and sensitivity (Han et al., 2017; Fronczek et al., 2023).

Despite the well-documented physiological link between vitamin D and insulin function, the impact of vitamin D supplementation on reducing the risk of T2DM remains inconclusive. While some meta-analyses suggest that supplementation lowers fasting blood glucose, circulating insulin levels, and insulin resistance markers such as HOMA-IR (Asbaghi et al., 2019; Sindhughosa et al., 2022), other studies present conflicting findings (Pieńkowska et al., 2023; Pittas et al., 2019).

4.1.1. Progress and remaining challenges

These discrepancies between mechanistic plausibility, epidemiological associations, and clinical trial outcomes highlight the unresolved nature of vitamin D's role in glucose metabolism. It remains unclear whether vitamin D deficiency directly contributes to insulin resistance or merely reflects underlying pathophysiological states such as chronic inflammation, poor metabolic health, or excess adiposity. While vitamin D status may function as a risk marker for insulin resistance and T2DM—particularly in obese individuals—its utility as a therapeutic target remains uncertain. The challenge moving forward lies in identifying specific subpopulations that may benefit from supplementation and clarifying the threshold at which deficiency becomes clinically meaningful.

4.2. Dyslipidemia

Vitamin D plays a multifaceted role in lipid metabolism and adipose tissue biology (Melguizo-Rodríguez et al., 2021). Through its nuclear receptor, VDR, expressed in adipocytes, vitamin D regulates genes involved in adipogenesis, lipolysis, and inflammatory signaling. Deficiency in vitamin D has been shown to increase parathyroid hormone (PTH) levels, which enhances intracellular calcium influx in adipocytes, favoring lipogenesis and impairing lipolysis—mechanisms that may contribute to both adipose expansion and dyslipidemia in obesity (Argano et al., 2023).

Several mechanistic pathways have been proposed through which vitamin D influences systemic lipid homeostasis. These include modulation of bile acid synthesis, suppression of hepatic lipogenesis, inhibition of lecithin-cholesterol acyltransferase (LCAT), and enhancement of calcium-mediated lipid absorption and cholesterol excretion. Such mechanisms suggest a potential role for vitamin D in regulating triglycerides (TGs), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) levels (Gholamzad et al., 2023; Al Refaie et al., 2024; Huang et al., 2023).

4.2.1. Progress and evidence

Numerous observational studies support an inverse relationship between serum 25(OH)D levels and markers of dyslipidemia, particularly LDL-C and TGs. A recent meta-analysis involving over 8000 overweight and obese individuals reported that vitamin D

deficiency was associated with elevated TGs, LDL-C, and total cholesterol, and reduced HDL-C (Al Refaie et al., 2024; Huang et al., 2023). These findings support a potential protective role for sufficient vitamin D levels in mitigating atherogenic lipid profiles.

4.2.2. Remaining challenges

Despite the consistent observational evidence, interventional studies involving vitamin D supplementation have yielded inconclusive or inconsistent effects on lipid parameters. While some trials demonstrate modest improvements, others fail to show significant changes, even in vitamin D-deficient individuals (Al Refaie et al., 2024). These discrepancies raise questions about the causality and mechanistic relevance of vitamin D in lipid regulation. Confounding variables—such as baseline vitamin D status, genetic polymorphisms, duration and dose of supplementation, and underlying metabolic health—may partially explain these inconsistencies. Moreover, it remains unclear whether vitamin D directly modulates lipid metabolism or whether observed associations are epiphenomena of broader metabolic dysregulation in obesity.

4.3. Hypertension and cardiovascular risk

Vitamin D deficiency has been implicated in the pathogenesis of hypertension and cardiovascular disease, particularly among individuals with obesity. One of the most frequently cited mechanisms involves the regulatory role of vitamin D in the renin-angiotensin-aldosterone system (RAAS), a key pathway in blood pressure homeostasis.

4.3.1. Proposed mechanisms linking vitamin D to blood pressure regulation

Vitamin D regulates RAAS by inhibiting renin gene expression, thereby reducing renin synthesis and preventing excessive activation of the system. When vitamin D levels are sufficient, RAAS remains balanced, ensuring proper blood pressure regulation. However, in vitamin D deficiency, this inhibition is lost, leading to overproduction of renin, which in turn increases angiotensin II levels. Angiotensin II causes vasoconstriction and stimulates aldosterone release, promoting fluid and salt retention—both of which contribute to elevated blood pressure. As a result, persistent RAAS overactivation due to low vitamin D levels can lead to hypertension, increasing the risk of cardiovascular diseases (Jorge et al., 2018; Han et al., 2022).

4.3.2. Observational findings and supplementation studies

Epidemiological studies consistently report an inverse relationship between serum 25(OH)D levels and both systolic and diastolic blood pressure, particularly in obese cohorts. Cross-sectional and cohort studies have linked vitamin D deficiency to increased prevalence and severity of hypertension, lending support to its role as a cardiovascular risk modifier (Sánchez-Ramírez et al., 2022; Zhang et al., 2020). Despite this theoretical link, randomized controlled trials investigating the effects of vitamin D supplementation on blood pressure have produced largely negative or inconclusive results. Most trials fail to demonstrate significant reductions in blood pressure or RAAS activity following vitamin D repletion, even among individuals with baseline deficiency (McMullan et al., 2017; Jensen et al., 2023; Zittermann et al., 2018).

4.3.3. Progress and remaining challenges

Despite consistent epidemiological associations and mechanistic plausibility, clinical trials of vitamin D supplementation have largely failed to demonstrate meaningful antihypertensive effects—particularly in obese individuals with coexisting hypertension. This discrepancy between observational and interventional findings raises critical questions regarding causality and therapeutic relevance. While vitamin D deficiency may function as a cardiovascular risk marker, it remains uncertain whether it plays a direct causal role or merely reflects underlying pathophysiological processes such as inflammation, metabolic dysregulation, and excess adiposity. Consequently, supplementation alone may be insufficient as an antihypertensive strategy in the multifactorial context of obesity.

4.4. Bone and mineral health

Vitamin D plays a pivotal role in calcium and phosphorus homeostasis and in the process of skeletal mineralization. Its active form, calcitriol (1,25-dihydroxyvitamin D), facilitates the intestinal absorption of dietary calcium and phosphate, both of which are essential for bone mineral deposition (Deluca, 2004). In the setting of vitamin D deficiency, inadequate absorption of calcium and phosphate from the gastrointestinal tract leads to hypocalcemia and hypophosphatemia, which in turn trigger compensatory hyperparathyroidism (Lips, 2001). Elevated parathyroid hormone (PTH) levels stimulate osteoclastogenesis and bone resorption in an attempt to mobilize skeletal calcium stores, while concurrently inhibiting osteoblast activity (Lips, 2001).

Beyond its role in mineral supply, vitamin D directly influences bone cells through the vitamin D receptor (VDR), which is expressed by osteoblasts, osteocytes, and osteoclast precursors (Deluca, 2004). Adequate calcitriol levels promote osteoblastic maturation, stimulate osteocalcin production, and attenuate excessive PTH-driven osteoclast activity. Additionally, vitamin D exerts important extra skeletal effects that indirectly support bone health, notably by enhancing muscle function. A classic manifestation of severe vitamin D deficiency is proximal muscle weakness and atrophy (Dzik et al., 2019), which heightens the risk of falls. Consequently, vitamin D deficiency can impair bone strength through multiple pathways such as elevated risk of falls due to muscle weakness and mediating the effect of proinflammatory cytokines on bone metabolism together constituting a multifaceted threat to skeletal integrity (Laird et al., 2010).

As previously noted in this review, many individuals with obesity also present with coexisting vitamin D deficiency (Pereira-Santos et al., 2015; Vimaleswaran et al., 2013). Obesity influences the skeleton through interlinked hormonal, mechanical, and inflammatory

pathways. Increased body mass enhances mechanical loading, stimulates bone formation, and often results in higher bone mineral density (BMD) (Salamat et al., 2016). In addition, aromatization of androgens to estrogens within adipose tissue elevates circulating estrogen levels (Longcope et al., 1986), which can promote bone formation and reduce bone resorption. Adipose tissue also functions as an active endocrine organ, secreting adipokines that regulate bone metabolism. Leptin, produced mainly by white adipose tissue, can promote osteoblast proliferation, differentiation, and mineralization, while inhibiting osteoclast formation through increased osteoprotegerin (OPG) expression and modulation of the receptor activator of NF-kB (RANK)/RANK/OPG pathway (Karsenty, 2006). However, these effects are not uniformly beneficial. Excessive adiposity—especially visceral fat—produces pro-inflammatory cytokines such as TNF-α and IL-6, which stimulate osteoclast activity and impair osteoblast function (Forte et al., 2023). Obesity is also associated with greater bone marrow adiposity, which can drive mesenchymal stem cells toward adipocyte rather than osteoblast differentiation (Benova and Tencerova, 2020), thereby reducing bone formation potential. Low vitamin D levels are common in obesity (Pereira-Santos et al., 2015) and can lead to secondary hyperparathyroidism, further promoting bone resorption (Lips, 2001). Thus, while obesity may contribute to higher BMD through mechanical and hormonal influences, chronic obesity—particularly with metabolic dysregulation—has features that can compromise bone integrity and increase fracture risk (Hou et al., 2020). In fact, In a cross-sectional study of 679 postmenopausal women, obese participants had significantly higher BMD than non-obese women but did not have a lower risk of fragility fractures; notably, type 2 diabetes mellitus in obese women was associated with a markedly higher risk of non-vertebral fractures (De Tejada-Romero et al., 2022). Similar patterns were observed in the multinational Global Longitudinal Study of Osteoporosis in Women (GLOW), which followed 44,534 postmenopausal women from 10 countries. In GLOW, overall fracture prevalence (222 vs 227 per 1000) and 2-year incidence (61.7 vs 66.0 per 1000) were comparable between obese and non-obese women. Site-specific analysis showed that obesity increased the risk of ankle fractures (OR 1.5, 95 % CI 1.2–1.9) and upper leg fractures (OR 1.7, 95 % CI 1.1–2.5) while lowering the risk of wrist fractures (OR 0.8, 95 % CI 0.6–1.0) (Compston et al., 2011). Together, these findings indicate that obesity confers a heterogeneous fracture risk profile that varies by skeletal site and comorbid conditions, challenging the notion of a uniformly protective effect.

4.4.1. Progress and remaining challenge

Although the links between vitamin D deficiency and skeletal outcomes (Lips, 2001; Laird et al., 2010) and, separately, between obesity and skeletal outcomes are well described (De Tejada-Romero et al., 2022; Compston et al., 2011), we did not identify studies explicitly designed to evaluate bone health in individuals who are both obese and vitamin D–deficient, nor studies that prespecify and test interaction between these exposures on fracture or microarchitectural endpoints. Most cohorts adjust for one factor while modeling the other, which can obscure any joint effect.

Mechanistically, a combined detriment is credible. Obesity influences bone through inflammatory cytokine signaling, expansion of marrow adiposity, and shifts in mesenchymal lineage allocation away from osteoblastogenesis (Forte et al., 2023; Benova and Tencerova, 2020; Hou et al., 2020), whereas vitamin D deficiency compromises calcium–phosphate homeostasis, induces secondary hyperparathyroidism with high turnover, and impairs muscle function (Lips, 2001; Dzik et al., 2019; Laird et al., 2010). Because these pathways are not redundant, their coexistence should impose at least an additive burden and may plausibly be synergistic—producing risk greater than the sum of individual effects. Future research should be specifically designed to examine the combined impact of obesity and vitamin D deficiency on bone health, rather than treating them as separate, unrelated factors. Such studies should recruit enough participants to allow meaningful comparisons between groups, consider differences in body composition and metabolic status, and include outcomes that reflect both bone quantity and quality, such as fracture rates, bone turnover markers, and advanced imaging of bone microarchitecture.

5. Discussion and conclusion

The intersection between obesity and vitamin D deficiency represents a critical, multifactorial nexus with both biological complexity and clinical importance. Cumulative epidemiological evidence consistently demonstrates a robust inverse association between adiposity and circulating 25[OH]D levels. This relationship is no longer viewed as merely correlative; genetic studies employing Mendelian randomization have confirmed a unidirectional causal link, indicating that obesity contributes to reduced vitamin D status rather than vice versa.

Mechanistic studies have advanced our understanding of this relationship, identifying three principal pathways: volumetric dilution, sequestration in adipose tissue, and impaired hepatic hydroxylation of vitamin D due to obesity-related downregulation of CYP2R1. These mechanisms are not mutually exclusive; instead, they act synergistically to suppress circulating vitamin D in obese individuals. While volumetric dilution is well-established, the physiological accessibility of sequestered vitamin D, especially during weight loss, remains unclear. Additionally, altered hepatic metabolism introduces a third, less visible layer of complexity that requires further exploration.

From a metabolic standpoint, vitamin D deficiency may act as both a marker and modifier of disease. As detailed in this review, low vitamin D status is linked to insulin resistance, dyslipidemia, and hypertension—three cardinal features of the metabolic syndrome. Mechanistically, vitamin D influences pancreatic β-cell function, insulin sensitivity, and inflammation, and regulates lipid and RAAS pathways. However, the progress in understanding these pathways contrasts with the remaining challenges in translating this knowledge into effective interventions.

One of the key unresolved issues is the inconsistency between observational and interventional findings. While observational studies suggest a protective role of vitamin D against metabolic dysregulation, randomized controlled trials of supplementation have often failed to show meaningful clinical benefit in terms of glycemic control, lipid regulation, or blood pressure reduction. These

discrepancies highlight the possibility that vitamin D deficiency, though mechanistically relevant, may reflect a broader metabolic milieu rather than serve as a standalone therapeutic target.

Evidence on the combined effects of obesity and vitamin D deficiency on bone health is lacking, as most studies assess these factors separately. Biological pathways suggest their coexistence could have additive or even synergistic detrimental effects. Obesity and vitamin D deficiency impair bone health via distinct, non-redundant mechanisms affecting structure, metabolism, and muscle function. Future studies should directly test their joint impact using robust designs, adequate sample sizes, and comprehensive bone health outcomes.

Another important consideration is dosing strategy. Standard vitamin D supplementation regimens—often fixed-dose and not adjusted for body weight—may be insufficient to overcome the altered kinetics seen in obesity. Emerging evidence supports BMI-based or weight-adjusted dosing as a more effective approach, particularly in the context of volumetric dilution and fat sequestration. Nonetheless, optimal dosing thresholds, safety margins, and long-term outcomes remain poorly defined.

Ultimately, the clinical approach to vitamin D deficiency in obesity must evolve beyond routine correction of serum levels toward a deeper understanding of its metabolic significance, therapeutic limitations, and individualized optimization.

CRediT authorship contribution statement

Reem J. Al Argan: Writing – review & editing, Writing – original draft, Validation, Supervision, Methodology, Investigation, Data curation, Conceptualization. **Safi G. Alqatari:** Writing – review & editing, Writing – original draft, Validation, Methodology, Investigation, Data curation, Conceptualization. **Abrar J. Alwaheed:** Writing – review & editing, Writing – original draft, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Manal A. Hasan:** Writing – review & editing, Writing – original draft, Supervision, Resources, Methodology, Investigation, Data curation. **Shaya Y. AlQahtani:** Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation, Data curation. **Mohammed D. Al Shubbar:** Writing – review & editing, Writing – original draft, Supervision, Software, Methodology, Investigation, Data curation, Conceptualization. **Abdullah H. Alnasser:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Conceptualization. **Safia M. Al Abbas:** Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Data curation, Conceptualization. **Noor H. AlYousef:** Writing – review & editing, Writing – original draft, Methodology, Data curation.

Informed consent statement

Not applicable.

Institutional review board statement

Not applicable.

Declaration of AI-assisted technologies in the writing process

During the preparation of this manuscript, the authors used ChatGPT-4o (OpenAI, 2024) for the purposes of checking grammar, enhancing clarity, and improving the scientific writing style of the article. The authors have thoroughly reviewed and edited the generated output and take full responsibility for the content of this publication.

Funding

This research received no external funding. The APC was funded by the authors.

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.

Data availability

No new data were created or analyzed in this study. Data sharing is not applicable to this article.

References

Al Refaie, A., Baldassini, L., Mondillo, C., De Vita, M., Giglio, E., Tarquini, R., et al., 2024. Vitamin D and dyslipidemia: is there really a link? A narrative review. Nutrients 16 (8), 1144.

Alzohily, B., AlMenhali, A., Gariballa, S., Munawar, N., Yasin, J., Shah, I., 2024. Unraveling the complex interplay between obesity and vitamin D metabolism. Sci. Rep. 14 (1), 7583.

Argano, C., Mirarchi, L., Amodeo, S., Orlando, V., Torres, A., Corrao, S., 2023. The role of vitamin D and its molecular bases in insulin resistance, diabetes, metabolic syndrome, and cardiovascular disease: state of the art. IJMS 24 (20), 15485.

Asbaghi, O., Khosroshahi, M., Kashkooli, S., Abbasnezhad, A., 2019. Effect of calcium-vitamin D Co-Supplementation on insulin, insulin sensitivity, and glycemia: a systematic review and meta-analysis of randomized clinical trials. Horm. Metab. Res. 51 (5), 288–295.
Bennour, I., Haroun, N., Sicard, F., Mounien, L., Landrier, J.F., 2022. Vitamin D and obesity/adiposity—A brief overview of recent studies. Nutrients 14 (10), 2049.
Benova, A., Tencerova, M., 2020. Obesity-induced changes in bone marrow homeostasis. Front. Endocrinol. 11, 294. https://doi.org/10.3389/fendo.2020.00294.
Bolland, M.J., Grey, A.B., Ames, R.W., Mason, B.H., Horne, A.M., Gamble, G.D., et al., 2007. The effects of seasonal variation of 25-hydroxyvitamin D and fat mass on a diagnosis of vitamin D sufficiency. Am. J. Clin. Nutr. 86 (4), 959–964.
Buyukinan, M., Ozen, S., Kokkun, S., Saz, E.U., 2012. The relation of vitamin D deficiency with puberty and insulin resistance in Obese children and adolescents. J. Pediatric Endocrinol. Metabolism. 25 (1–2). Available from: https://www.degruyter.com/document/doi/10.1515/jpem-2011-0426/html. (Accessed 18 March 2025).
Carrelli, A., Bucovsky, M., Horst, R., Cremers, S., Zhang, C., Bessler, M., et al., 2017. Vitamin D storage in adipose tissue of Obese and normal weight women. J. Bone Miner. Res. 32 (2), 237–242.
Chakhtoura, M.T., Nakhoul, N., Akl, E.A., Mantzoros, C.S., El Hajj Fuleihan, G.A., 2016. Guidelines on vitamin D replacement in bariatric surgery: identification and systematic appraisal. Metabolism 65 (4), 586–597.
Cheng, J.B., Levine, M.A., Bell, N.H., Mangelsdorf, D.J., Russell, D.W., 2004. Genetic evidence that the human CYP2R1 enzyme is a key vitamin D 25-hydroxylase. Proc. Natl. Acad. Sci. U.S.A 101 (20), 7711–7715.
Cominacini, M., Fumaneri, A., Ballerini, L., Braggio, M., Valenti, M.T., Dalle Carbonare, L., 2023. Unraveling the connection: visceral adipose tissue and vitamin D levels in obesity. Nutrients 15 (19), 4259.
Compston, J.E., Watts, N.B., Chapurlat, R., Cooper, C., Boonen, S., Greenspan, S., et al., 2011. Obesity is not protective against fracture in postmenopausal women: glow. Am. J. Med. 124 (11), 1043–1050.
Coupaye, M., Breuil, M.C., Rivière, P., Castel, B., Bogard, C., Dupré, T., et al., 2013. Serum vitamin D increases with weight loss in obese subjects 6 months after Roux-en-Y gastric bypass. Obes. Surg. 23 (4), 486–493.
De Tejada-Romero, M.J.G., Saavedra-Santana, P., De La Rosa-Fernández, F., Suárez-Ramírez, N., Martín-Martínez, A., Del Rosario, F.M., et al., 2022. Effect of obesity on fragility fractures, BMD and vitamin D levels in postmenopausal women. Influence of type 2 diabetes mellitus. Acta Diabetol. 59 (9), 1201–1208.
Deluca, H., 2004. Overview of general physiologic features and functions of vitamin D. Am. J. Clin. Nutr. 80 (Suppl. l), 1689S–1696S.
Delvin, E.E., Lambert, M., Levy, E., O'Loughlin, J., Mark, S., Gray-Donald, K., et al., 2010. Vitamin D status is modestly associated with glycemia and indicators of lipid metabolism in French-Canadian children and adolescents. J. Nutr. 140 (5), 987–991.
Drincic, A., Fuller, E., Heaney, R.P., Armas, L.A.G., 2013. 25-Hydroxyvitamin D response to graded vitamin D_3 supplementation among Obese adults. J. Clin. Endocrinol. Metabol. 98 (12), 4845–4851.
Dzik, K.P., Skrobot, W., Kaczor, K.B., Flis, D.J., Karnia, M.J., Libionka, W., et al., 2019. Vitamin D deficiency is associated with muscle atrophy and reduced mitochondrial function in patients with chronic low back pain. Oxid. Med. Cell. Longev. 2019, 6835341. https://doi.org/10.1155/2019/6835341.
Forte, Y.S., Renovato-Martins, M., Barja-Fidalgo, C., 2023. Cellular and molecular mechanisms associating obesity to bone loss. Cells 12 (4), 521. https://doi.org/10.3390/cells12040521.
Fronczek, M., Osadnik, T., Banach, M., 2023. Impact of vitamin D receptor polymorphisms in selected metabolic disorders. Curr. Opin. Clin. Nutr. Metab. Care 26 (4), 316–322.
Fuentes-Barría, H., Aguilera-Eguía, R., Flores-Fernández, C., Angarita-Davila, L., Rojas-Gómez, D., Alarcón-Rivera, M., et al., 2025. Vitamin D and type 2 diabetes mellitus: molecular mechanisms and clinical implications—A narrative review. IJMS 26 (5), 2153.
Gallagher, J.C., Yalamanchili, V., Smith, L.M., 2013. The effect of vitamin D supplementation on serum 25OHD in thin and obese women. J. Steroid Biochem. Mol. Biol. 136, 195–200.
Gao, Z., Liang, Y., Huang, S., Wu, Z., Li, M., Yang, J., 2023. Prevalence and associated factors of vitamin D deficiency after Roux-en-Y gastric bypass: a systematic review and meta-analysis. Int. J. Surgery. Available from: https://journals.lww.com/10.1097/JS9.0000000000000732. (Accessed 12 May 2025).
Gholamzad, A., Khakpour, N., Kabipour, T., Gholamzad, M., 2023. Association between serum vitamin D levels and lipid profiles: a cross-sectional analysis. Sci. Rep. 13 (1), 21058.
Hajhashemy, Z., Shahdadian, F., Ziaei, R., Saneei, P., 2021. Serum vitamin D levels in relation to abdominal obesity: a systematic review and dose–response meta-analysis of epidemiologic studies. Obes. Rev. 22 (2), e13134.
Han, F fei, Lv, Y li, Gong, L li, Liu, H., Wan, Z rui, Liu, L hong, 2017. VDR gene variation and insulin resistance related diseases. Lipids Health Dis. 16 (1), 157.
Han, L., Xu, X.J., Zhang, J.S., Liu, H.M., 2022. Association between vitamin D deficiency and levels of renin and angiotensin in essential hypertension. In: Sainaghi, P. P. (Ed.), Int. J. Clin. Pract. 1–6.
Himbert, C., Ose, J., Delphan, M., Ulrich, C.M., 2017. A systematic review of the interrelation between diet- and surgery-induced weight loss and vitamin D status. Nutr. Res. 38, 13–26.
Hou, J., He, C., He, W., Yang, M., Luo, X., Li, C., 2020. Obesity and bone health: a complex link. Front. Cell Dev. Biol. 8, 600181.
Huang, X., Yang, Y., Jiang, Y., Zhou, Z., Zhang, J., 2023. Association between vitamin D deficiency and lipid profiles in overweight and obese adults: a systematic review and meta-analysis. BMC Public Health 23 (1), 1653.
Jensen, N.S., Wehland, M., Wise, P.M., Grimm, D., 2023. Latest knowledge on the role of vitamin D in hypertension. IJMS 24 (5), 4679.
Jorge, A.J.L., Cordeiro, J.R., Rosa, M.L.G., Bianchi, D.B.C., 2018. Vitamin D deficiency and cardiovascular diseases. Int. J. Cardiovascular Sci. Available from: https://www.scielo.br/scielo.php?script=sci_arttext&pid=S2359-56472018000400422. (Accessed 18 March 2025).
Kabadi, S.M., Lee, B.K., Liu, L., 2012. Joint effects of obesity and vitamin D insufficiency on insulin resistance and type 2 diabetes. Diabetes Care 35 (10), 2048–2054.
Karampela, I., Sakelliou, A., Vallianou, N., Christodoulatos, G.S., Magkos, F., Dalamaga, M., 2021. Vitamin D and obesity: current evidence and controversies. Curr Obes Rep 10 (2), 162–180.
Karatas, 2013. Vitamin D levels in overweight/obese adults with and without metabolic syndrome. J Endocrinol Metab [Internet]. Available froJ Endocrinol Metabm: http://www.jofem.org/index.php/jofem/article/view/182. (Accessed 6 March 2025).
Karsenty, G., 2006. Convergence between bone and energy homeostases: leptin regulation of bone mass. Cell Metab. 4 (5), 341–348. https://doi.org/10.1016/j.cmet.2006.10.008.
Kirsty Forsythe, L., Livingstone, M.B.E., Barnes, M.S., Horigan, G., McSorley, E.M., Bonham, M.P., et al., 2012. Effect of adiposity on vitamin D status and the 25-hydroxycholecalciferol response to supplementation in healthy young and older Irish adults. Br. J. Nutr. 107 (1), 126–134.
Laird, E., Ward, M., McSorley, E., Strain, J.J., Wallace, J., 2010. Vitamin D and bone health; potential mechanisms. Nutrients 2 (7), 693–724.
Lespessailles, E., Toumi, H., 2017. Vitamin D alteration associated with obesity and bariatric surgery. Exp Biol Med (Maywood) 242 (10), 1086–1094.
Lips, P., 2001. Vitamin D deficiency and secondary hyperparathyroidism in the elderly: consequences for bone loss and fractures and therapeutic implications. Endocr. Rev. 22 (4), 477–501. https://doi.org/10.1210/edrv.22.4.0437.
Longcope, C., Baker, R., Johnston Jr., C.C., 1986. Androgen and estrogen metabolism: relationship to obesity. Metabolism 35 (3), 235–237. https://doi.org/10.1016/0026-0495(86)90206-4.
Lotfi-Dizaji, L., Mahboob, S., Aliashrafi, S., Vaghef-Mehrabany, E., Ebrahimi-Mameghani, M., Morovati, A., 2019. Effect of vitamin D supplementation along with weight loss diet on meta-inflammation and fat mass in obese subjects with vitamin D deficiency: a double-blind placebo-controlled randomized clinical trial. Clin. Endocrinol. 90 (1), 94–101.
Mai, X.M., Chen, Y., Camargo, C.A., Langhammer, A., 2012. Cross-sectional and prospective cohort study of serum 25-Hydroxyvitamin D level and obesity in adults: the HUNT study. Am. J. Epidemiol. 175 (10), 1029–1036.
Mallard, S.R., Howe, A.S., Houghton, L.A., 2016. Vitamin D status and weight loss: a systematic review and meta-analysis of randomized and nonrandomized controlled weight-loss trials. Am. J. Clin. Nutr. 104 (4), 1151–1159.
Mason, C., Xiao, L., Imayama, I., Duggan, C.R., Bain, C., Foster-Schubert, K.E., et al., 2011. Effects of weight loss on serum vitamin D in postmenopausal women. Am. J. Clin. Nutr. 94 (1), 95–103.

Masood, B., Moorthy, M., 2023. Causes of obesity: a review. Clin. Med. 23 (4), 284–291.
McMullan, C.J., Borgi, L., Curhan, G.C., Fisher, N., Forman, J.P., 2017. The effect of vitamin D on renin–angiotensin system activation and blood pressure: a randomized control trial. J. Hypertens. 35 (4), 822–829.
Melguizo-Rodríguez, L., Costela-Ruiz, V.J., García-Recio, E., De Luna-Bertos, E., Ruiz, C., Illescas-Montes, R., 2021. Role of vitamin D in the metabolic syndrome. Nutrients 13 (3), 830.
Moslemi, E., Musazadeh, V., Kavyani, Z., Naghsh, N., Shoura, S.M.S., Dehghan, P., 2022. Efficacy of vitamin D supplementation as an adjunct therapy for improving inflammatory and oxidative stress biomarkers: an umbrella meta-analysis. Pharmacol. Res. 186, 106484.
Mutt, S.J., HyppÃ¶nen, E., Saarnio, J., Jãrvelin, M.R., Herzig, K.H., 2014. Vitamin D and adipose tissueâ€"more than storage. Front Physiol [Internet] 5. Available from: http://journal.frontiersin.org/article/10.3389/fphys.2014.00228/abstract. (Accessed 10 March 2025).
Obesity [Internet], 2021. World Health Organization. Available from: https://www.who.int/news-room/facts-in-pictures/detail/6-facts-on-obesity#:~:text=,2016%2C%20and%20650%20million%20obese. (Accessed 6 March 2025).
Palacios, C., Gonzalez, L., 2014. Is vitamin D deficiency a major global public health problem? J. Steroid Biochem. Mol. Biol. 144, 138–145.
Pannu, P.K., Zhao, Y., Soares, M.J., 2016. Reductions in body weight and percent fat mass increase the vitamin D status of obese subjects: a systematic review and metaregression analysis. Nutr. Res. 36 (3), 201–213.
Pereira-Santos, M., Costa, P.R.F., Assis, A.M.O., Santos, C.A.S.T., Santos, D.B., 2015. Obesity and vitamin D deficiency: a systematic review and meta-analysis. Obes. Rev. 16 (4), 341–349.
Perticone, M., Maio, R., Sciacqua, A., Suraci, E., Pinto, A., Pujia, R., et al., 2019. Ketogenic diet-induced weight loss is associated with an increase in vitamin D levels in Obese adults. Molecules 24 (13), 2499.
Peterson, C.A., Tosh, A.K., Belenchia, A.M., 2014. Vitamin D insufficiency and insulin resistance in obese adolescents. Therapeutic Adv. Endocrinol 5 (6), 166–189.
Pieńkowska, A., Janicka, J., Duda, M., Dzwonnik, K., Lip, K., Mędza, A., et al., 2023. Controversial impact of vitamin D supplementation on reducing insulin resistance and prevention of type 2 diabetes in patients with prediabetes: a systematic review. Nutrients 15 (4), 983.
Pittas, A.G., Dawson-Hughes, B., Sheehan, P., Ware, J.H., Knowler, W.C., Aroda, V.R., et al., 2019. Vitamin D supplementation and prevention of type 2 diabetes. N. Engl. J. Med. 381 (6), 520–530.
Plesner, J.L., Dahl, M., Fonvig, C.E., Nielsen, T.R.H., Kloppenborg, J.T., Pedersen, O., et al., 2018. Obesity is associated with vitamin D deficiency in Danish children and adolescents. J. Pediatr. Endocrinol. Metab. 31 (1), 53–61.
Rosenstreich, S.J., Rich, C., Volwiler, W., 1971. Deposition in and release of vitamin D3 from body fat: evidence for a storage site in the rat. J. Clin. Investig. 50 (3), 679–687.
Sadat-Ali, M., AlTabash, K.W., Al-Turki, H.A., AlMousa, S.A., AlSayed, H.N., 2021. Time out: should vitamin D dosing be based on patient's body mass index (BMI): a prospective controlled study. J. Nutr. Sci. 10, e106.
Salamat, M.R., Salamat, A.H., Janghorbani, M., 2016. Association between obesity and bone mineral density by gender and menopausal status. Endocrinol Metab (Seoul) 31 (4), 547–558. https://doi.org/10.3803/EnM.2016.31.4.547.
Sánchez-Ramírez, C.A., Cortés Álvarez, S.I., Flores-Ruelas, Y., Del Toro-Equihua, M., Pérez-Manzo, L., Delgado-Enciso, I., 2022. Serum 25-Hydroxyvitamin D correlates with systolic blood pressure in obese male schoolchildren. Nutr Hosp [Internet]. Available from: https://www.nutricionhospitalaria.org/articles/03911/show. (Accessed 22 July 2025).
Shantavasinkul, P.C., Nimitphong, H., 2022. Vitamin D and visceral obesity in humans: what should Clinicians know? Nutrients 14 (15), 3075.
Sindhughosa, D.A., Wibawa, I.D.N., Mariadi, I.K., Somayana, G., 2022. Additional treatment of vitamin D for improvement of insulin resistance in non-alcoholic fatty liver disease patients: a systematic review and meta-analysis. Sci. Rep. 12 (1), 7716.
Sneve, M., Figenschau, Y., Jorde, R., 2008. Supplementation with cholecalciferol does not result in weight reduction in overweight and obese subjects. Eur. J. Endocrinol. 159 (6), 675–684.
Szymczak-Pajor, I., Śliwińska, A., 2019. Analysis of association between vitamin D deficiency and insulin resistance. Nutrients 11 (4), 794.
Torun, E., Gönüllü, E., Özgen, İ.T., Cindemir, E., Öktem, F., 2013. Vitamin D deficiency and insufficiency in obese children and adolescents and its relationship with insulin resistance. Int. J. Endocrinol. 2013, 1–5.
Tzotzas, T., Papadopoulou, F.G., Tziomalos, K., Karras, S., Gastaris, K., Perros, P., et al., 2010. Rising serum 25-Hydroxy-Vitamin D levels after weight loss in Obese women correlate with improvement in insulin resistance. J. Clin. Endocrinol. Metabol. 95 (9), 4251–4257.
Vanlint, S., 2013. Vitamin D and obesity. Nutrients 5 (3), 949–956.
Vimaleswaran, K.S., Berry, D.J., Lu, C., Tikkanen, E., Pilz, S., Hiraki, L.T., et al., 2013. Causal relationship between obesity and vitamin D status: bi-directional mendelian randomization analysis of multiple cohorts. In: Minelli, C. (Ed.), PLoS Med. 10 (2), e1001383.
Vranić, L., Mikolašević, I., Milić, S., 2019. Vitamin D deficiency: consequence or cause of obesity? Medicina 55 (9), 541.
Wortsman, J., Matsuoka, L.Y., Chen, T.C., Lu, Z., Holick, M.F., 2000. Decreased bioavailability of vitamin D in obesity. Am. J. Clin. Nutr. 72 (3), 690–693.
Zhang, Y., Zhang, X., Wang, F., Zhang, W., Wang, C., Yu, C., et al., 2016. The relationship between obesity indices and serum vitamin D levels in Chinese adults from urban settings. Asia Pacific J. Clinical Nutrition [Internet]. Available from: https://search.informit.org/doi/abs/10.3316/ielapa.104380349214033.
Zhang, D., Cheng, C., Wang, Y., Sun, H., Yu, S., Xue, Y., et al., 2020. Effect of vitamin D on blood pressure and hypertension in the general population: an update meta-analysis of cohort studies and randomized controlled trials. Prev Chronic Dis [Internet], 17. Available from: http://www.cdc.gov/pcd/issues/2020/19_0307.htm. (Accessed 22 July 2025).
Zittermann, A., Ernst, J.B., Prokop, S., Fuchs, U., Dreier, J., Kuhn, J., et al., 2018. Effects of vitamin D supplementation on renin and aldosterone concentrations in patients with advanced heart failure: the EVITA trial. Int. J. Endocrinol. 2018, 1–10.