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Review

Vitamin D in Obesity: Mechanisms and Clinical Impact

Jitka Jirků [1,2,*], Zuzana Kršáková [1] and Jarmila Křížová [1,*]

[1] 3rd Department of Internal Medicine, Department of Endocrinology and Metabolism, General University Hospital in Prague—VFN, First Faculty of Medicine, Charles University, 12808 Prague, Czech Republic
[2] Nutrition Outpatient Clinic, 14000 Prague, Czech Republic
* Correspondence: info@nutricniambulance.cz (J.J.); jarmila.krizova@vfn.cz (J.K.)

Abstract

Obesity is a major global health challenge that substantially affects vitamin D metabolism and status. Numerous studies have consistently demonstrated an inverse relationship between body fat and serum 25-hydroxyvitamin D [25(OH)D] concentrations. Emerging evidence suggests that lower serum 25(OH)D in obesity largely reflects altered distribution and metabolism rather than a uniform state of true functional deficiency. Adipose tissue functions both as a storage compartment and as a metabolically active organ capable of modulating vitamin D handling. Mechanisms include the sequestration of vitamin D in fat, volumetric dilution across a larger body mass, and the local expression of enzymes involved in vitamin D metabolism. As a result, obese individuals typically exhibit a blunted increase in serum 25(OH)D in response to supplementation, consistent with altered pharmacokinetics and increased distribution volume. Weight loss, particularly the reduction in visceral fat, is associated with modest increases in circulating 25(OH)D, further supporting a distribution-based mechanism. Although low 25(OH)D levels in obesity have been linked to insulin resistance, inflammation, and metabolic syndrome, randomized controlled trials have not consistently demonstrated that supplementation improves clinically relevant outcomes in this population. Meta-analyses confirm that the increase in serum 25(OH)D after supplementation is smaller in obese individuals, indicating that higher doses are often required to achieve comparable levels to those in normal-weight subjects. Obesity thus represents a major determinant of vitamin D deficiency, highlighting the need for individualized supplementation strategies alongside weight management. Understanding the mechanistic basis for low 25(OH)D in obesity is essential for distinguishing true deficiency from altered distribution, informing clinical decisions, and optimizing interventions to maintain adequate vitamin D status and support metabolic health.

Keywords: vitamin D; obesity; 25-hydroxyvitamin D; supplementation; adipose tissue

Academic Editor: Juergen Vormann

Received: 5 December 2025
Revised: 21 January 2026
Accepted: 2 February 2026
Published: 6 February 2026

1. Introduction

Obesity and vitamin D deficiency are both highly prevalent worldwide and frequently coexist, sustaining long-standing interest in their potential biological and clinical interrelationship. Definitions of vitamin D deficiency and insufficiency in this review are based on current international guidelines (see below). Obesity is recognized as one of the strongest predictors of low circulating serum 25-hydroxyvitamin D [25(OH)D] concentrations, second only to limited sunlight exposure [1,2]. Numerous observational studies have consistently demonstrated an inverse association between measures of adiposity and serum 25(OH)D levels; however, despite the robustness of this relationship, its interpretation remains

controversial. A central unresolved issue is whether the reduced total serum 25(OH)D concentrations observed in individuals with obesity represent true vitamin D deficiency with impaired biological action, or whether they primarily reflect altered distribution, storage, and metabolism of vitamin D within an expanded body mass. Importantly, similar body mass index (BMI) values may correspond to markedly different proportions of visceral and subcutaneous adipose tissue, which differ substantially in metabolic activity and vitamin D handling. Moreover, total serum 25(OH)D—the most commonly used biomarker of vitamin D status—may not fully capture tissue availability or hormonal activity, particularly in conditions characterized by altered vitamin D-binding protein concentrations or an increased distribution volume. Several non-mutually exclusive mechanisms have been proposed to explain lower circulating 25(OH)D concentrations in obesity, including sequestration of vitamin D in adipose tissue, volumetric dilution across larger fat and lean mass compartments, and altered expression of enzymes involved in vitamin D metabolism. Mendelian randomization studies further suggest that increased adiposity causally lowers circulating 25(OH)D concentrations, whereas genetically determined low vitamin D status does not appear to cause obesity, challenging simplistic causal interpretations derived from observational data. Beyond its classical role in calcium and bone metabolism, vitamin D has been implicated in multiple pathways relevant to obesity-related metabolic disturbances, including insulin sensitivity, inflammation, and cardiovascular regulation. The active form, 1,25-dihydroxyvitamin D [1,25$(OH)_2$D], may contribute to limiting tissue damage and metabolic complications associated with excessive adiposity [1]. Nevertheless, large randomized controlled trials have largely failed to demonstrate consistent benefits of vitamin D supplementation on body weight, adiposity, or major cardiometabolic outcomes, raising questions about the clinical implications of correcting low 25(OH)D concentrations in individuals with obesity. The aim of this review is to critically synthesize current evidence on vitamin D metabolism in obesity, with particular emphasis on distinguishing altered distribution from true deficiency, evaluating the translational relevance of mechanistic and genetic studies, and assessing the clinical significance of supplementation. By integrating observational, mechanistic, genetic, and interventional data, this review seeks to provide a coherent framework for interpreting low 25(OH)D concentrations in obesity and for guiding rational clinical decision-making.

2. Adipose Tissue as a Dynamic Reservoir of Vitamin D

White adipose tissue (WAT) represents the predominant adipose depot in humans located in subcutaneous and visceral depots. Its development and maintenance depend on the nuclear receptor peroxisome proliferator-activated receptor gamma (PPARγ), which governs adipogenesis, regulates fatty acid storage and glucose metabolism. Brown adipose tissue (BAT) is a specialized adipose tissue subtype in mammals that functions primarily in thermoregulation. Activated BAT expresses the uncoupling protein 1 (UCP1) in the inner mitochondrial membrane, which uncouples substrate oxidation from ATP synthesis, resulting in enhanced substrate oxidation and thermogenesis [2].

Adipose tissue is also one of the major extraskeletal target organs of vitamin D. Expression of the gene encoding the vitamin D receptor (VDR), as well as key vitamin D–metabolizing enzymes, has been demonstrated in both preadipocytes and differentiated adipocytes within subcutaneous and visceral fat depots. Consequently, vitamin D can significantly influence adipose tissue biology, particularly through its active form, 1,25$(OH)_2$D, which plays an important role in adipocyte differentiation. The 1,25$(OH)_2$D–VDR complex, in association with the retinoid X receptor (RXR), regulates the expression of multiple adipocyte-related genes by binding to vitamin D response elements (VDREs) and acts through endocrine, autocrine, and paracrine pathways [3]. Collectively, these mechanisms

underscore adipose tissue as not merely a passive storage site but as a metabolically active endocrine organ responsive to vitamin D–dependent signaling. In this context, vitamin D accumulation in adipose tissue does not appear to represent irreversible sequestration; rather, adipose tissue functions as a dynamic storage compartment characterized by a slow but continuous exchange between adipose depots and circulation.

Rosenstreich et al. were the first to identify adipose tissue as a principal storage depot for vitamin D in 1971, using rats fed radiolabeled vitamin D_3 [4]. They showed that within 6 weeks of administration, 80% of the total body radioactivity was localized in adipose tissue, with more than half of it retaining chromatographic characteristics consistent with unmodified vitamin D [4]. These early findings established adipose tissue as the major extravascular storage site for vitamin D and prompted subsequent research in humans. In studies by Haeney involving adult women, total-body vitamin D consisted of approximately 65% native cholecalciferol and 35% 25(OH)D. Nearly three-quarters of the cholecalciferol was stored in fat, whereas 25(OH)D was more evenly distributed (20% in muscle, 30% in serum, 35% in fat, and 15% in other tissues) [5]. Lawson et al. developed a sensitive analytical method for detecting vitamin D in tissues and demonstrated substantial concentrations of vitamin D_3 (50–100 ng/g) in adipose samples obtained post-mortem from perirenal, pericardial, cervical, and axillary regions [6]. The study did not identify significant differences in adipose vitamin D_3 concentrations by sex, age, or season of sampling, but showed that vitamin D_3 is released from adipose tissue during deficiency, with an estimated half-life of 12 days [6]. These observations confirm that adipose tissue not only stores vitamin D but also releases it in a regulated manner depending on systemic vitamin D status. Didriksen et al. assessed vitamin D and 25(OH)D concentrations in subcutaneous adipose tissue using biopsy samples obtained before and after long-term supplementation (20,000 IU/week for 3–5 years) compared with placebo [7]. They observed not only a marked increase in the supplemented group but also quantified total mean adipose stores of 6.6 mg of vitamin D and 0.12 mg of 25(OH)D in supplemented individuals, compared with 0.95 mg and 0.08 mg, respectively, in controls [7].

These findings demonstrate that adipose tissue stores continue to accumulate with prolonged supplementation and may significantly contribute to long-term vitamin D availability. Notably, in some studies human perirenal adipose tissue has been characterized as BAT, suggesting that vitamin D may also be stored in BAT [8]. Adipose tissue also functions as a site of vitamin D metabolism, including both 25-hydroxylation and subsequent 1α-hydroxylation to the hormonally active calcitriol ($1,25(OH)_2D$), as well as the homeostatic catabolism of these metabolites via the enzyme CYP24A1. This supports the concept that adipose tissue acts not only as a reservoir but also as a metabolically active organ influencing systemic vitamin D homeostasis. The amount of intact vitamin D stored in adipose tissue does not correlate with circulating vitamin D or serum 25(OH)D concentrations. In contrast, serum 25(OH)D levels directly correlate with its concentrations in both visceral and subcutaneous fat depots [9–11].

3. Mechanisms Linking Obesity and Low 25(OH)D

When analyzing the reasons for the low levels of vitamin D in obese individuals, it is important to consider, among other factors, differences in lifestyle compared with non-obese individuals, including dietary habits, physical inactivity, and clothing choices. These lifestyle differences likely contribute to the high prevalence of vitamin D deficiency—commonly defined as serum 25(OH)D concentrations below 50 nmol/L—observed in overweight and obese populations. Several meta-analyses support this, with Pereira-Santos et al. reporting a 35% higher risk of deficiency in obese subjects, and Yao et al. finding a 3.4-fold greater likelihood of deficiency compared with non-obese participants [12,13].

Nevertheless, considerable heterogeneity exists across studies, particularly regarding definitions of obesity (e.g., BMI, body fat percentage, waist circumference), ethnic background, and fat distribution patterns (subcutaneous versus visceral), which may partly explain variations in the reported prevalence of deficiency.

3.1. Sequestration Hypothesis

When obese and non-obese participants were exposed to identical whole-body UVB irradiation or received a single oral dose of 50,000 IU of vitamin D, the subsequent increase in serum 25(OH)D concentrations were consistently attenuated in obese individuals [14]. Similarly, Didriksen et al., analyzing pooled data from three randomized trials using weekly supplementation of 40,000 IU for six months, demonstrated that individuals with higher BMI not only exhibited lower baseline 25(OH)D concentrations but also showed a blunted response to supplementation [15]. Gallagher et al. further evaluated seven different vitamin D doses (400–4800 IU/day) and observed a substantially greater increase in post-supplementation serum 25(OH)D concentrations in women with normal BMI (<25 kg/m^2) compared with those with obesity [16]. These findings support the concept that increased adiposity is associated with reduced responsiveness to vitamin D intake. According to Wortsman et al., intact vitamin D is sequestered within adipose tissue, thereby reducing its bioavailability for further metabolic conversion and systemic circulation [14]. Rather than representing irreversible sequestration, adipose tissue appears to function as a dynamic storage compartment characterized by a slow exchange between adipose depots and the circulation, which may nonetheless reduce the immediate bioavailability of vitamin D in individuals with obesity [14], (see Figure 1).

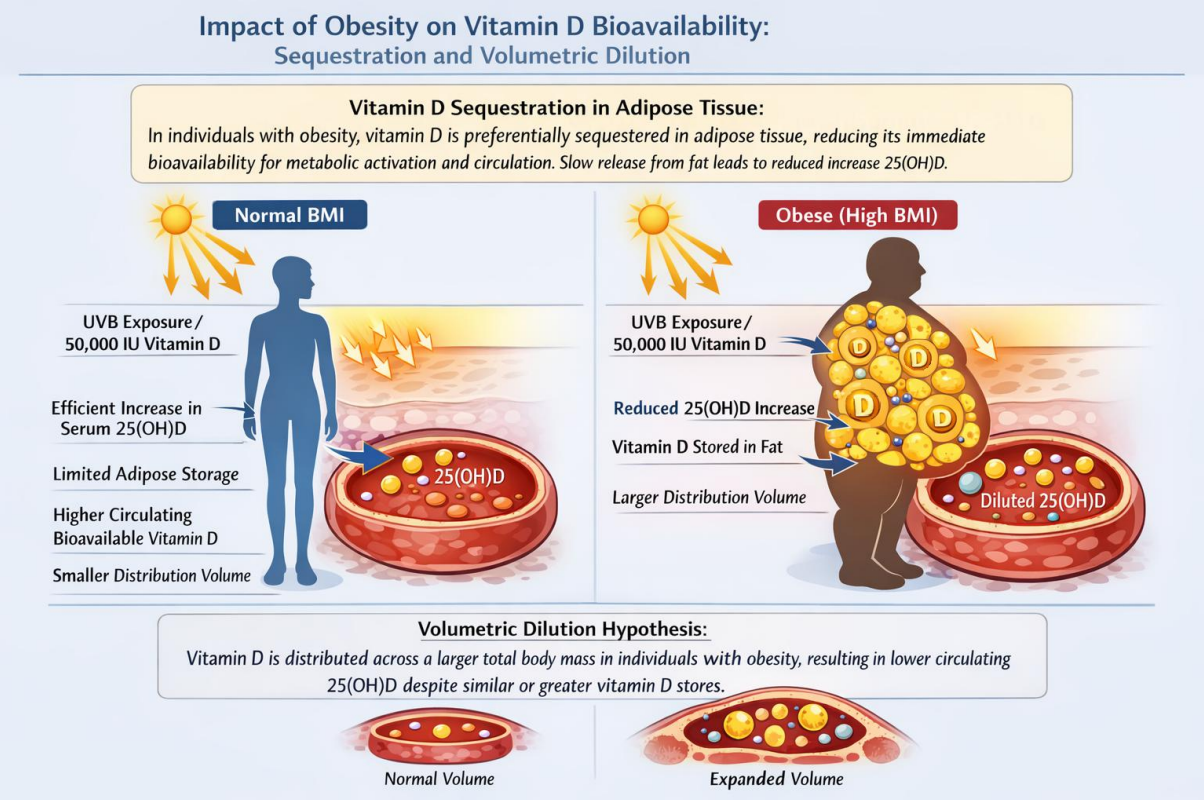

Figure 1. Schematic representation of the mechanisms underlying reduced vitamin D status in obesity. In individuals with obesity, vitamin D is sequestered in expanded adipose tissue and distributed across a larger body volume, leading to lower circulating 25(OH)D concentrations despite comparable UVB exposure or supplementation. Both adipose sequestration and volumetric dilution contribute to the attenuated serum vitamin D response.

3.2. Volumetric Dilution Hypothesis

Conversely, Heaney et al. reported that after adjustment for total body weight, fat mass was not a superior predictor of the serum 25(OH)D response to supplementation [17]. Their findings suggest that, in addition to adipose tissue, skeletal muscle represents an important reservoir for 25(OH)D. Accordingly, differences in post-supplementation 25(OH)D responses between obese and non-obese individuals may be better explained by variations in distribution volume rather than by adipose tissue mass alone [17]. This concept underlies the volumetric dilution hypothesis, whereby vitamin D is distributed across a larger total body mass—comprising both fat and lean compartments—in individuals with obesity.

Drincic et al. similarly proposed volumetric dilution as an alternative explanation for lower circulating 25(OH)D concentrations in obesity [18]. Supporting this notion, Carrelli et al. demonstrated that although obese individuals had greater total amounts of cholecalciferol stored in adipose tissue, the concentration per gram of fat did not differ significantly from that observed in normal-weight subjects [19]. A recent meta-analysis, primarily including studies from Europe and North America, showed that each 1 kg/m^2 increase in BMI was associated with an approximately 1.15% decrease in serum 25(OH)D concentrations. This inverse association was more pronounced in populations with limited UVB exposure, highlighting the contribution of lifestyle-related reductions in cutaneous vitamin D synthesis among individuals with obesity [20] (see Figure 1).

3.3. Polymorphisms of Vitamin D-Related Genes

In addition to altered distribution, impaired metabolic activation may further contribute to reduced vitamin D status in obesity. Studies have revealed associations between polymorphisms, VDRs, VDBP and CYP27B1 genes and BMI, obesity markers, or obesity itself [21,22]. For example, the expression of CYP27B1 in white adipose tissue has been reported to be lower in obese individuals compared with lean counterparts, potentially limiting local conversion to the active hormone $1,25(OH)_2D$ [9,23]. Mendelian randomization analyses using genes involved in vitamin D metabolism (VDBP, DHCR7, CYP2R1, and CYP24A1) as instrumental variables suggest that low 25(OH)D concentrations have little or no effect on BMI [20,24,25]. Interestingly, VDR gene polymorphisms may influence the amount of visceral adipose tissue and waist circumference in individuals supplemented with vitamin D [26]. Taken together, these findings suggest that both altered storage dynamics and reduced metabolic activation contribute to lower circulating vitamin D levels in obesity (see Figure 2).

If reduced serum 25(OH)D concentrations primarily reflect dilution across expanded fat and lean mass compartments, total circulating levels may underestimate vitamin D sufficiency at the tissue level. It therefore remains unclear whether the low serum 25(OH)D concentrations observed in obesity represent a true "functional" vitamin D deficiency or merely a biochemical finding. Approximately 99% of circulating 25(OH)D and $1,25(OH)_2D$ is bound to vitamin D-binding protein (DBP) or albumin. Similarly to other hormone-binding proteins, DBP serves both as a transporter and as a circulating reservoir, modulating the bioavailability of vitamin D metabolites to target tissues. Consequently, vitamin D sufficiency and biological activity may be more accurately reflected by free or bioavailable vitamin D concentrations rather than by total serum levels alone [27,28]. This interpretation is consistent with observations that individuals with obesity often maintain relatively preserved calcium homeostasis and parathyroid hormone responses despite low total serum 25(OH)D concentrations.

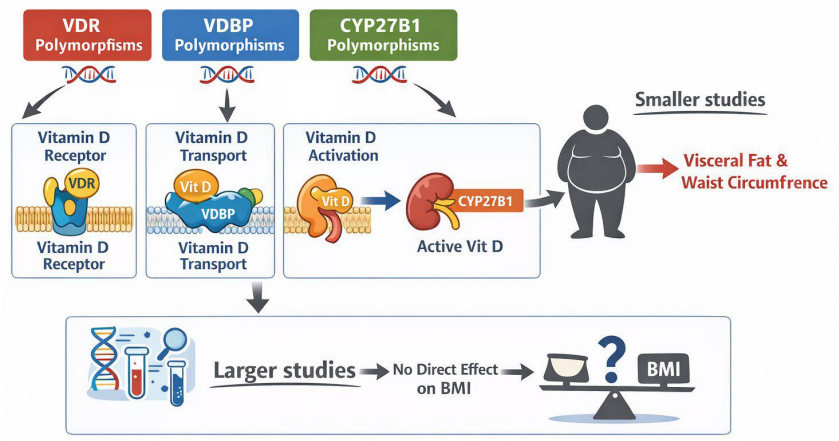

Figure 2. Genetic and molecular mechanisms influencing vitamin D metabolism in obesity. The infographic illustrates genetic factors related to vitamin D and their potential impact on obesity. It includes VDR, VDBP, CYP27B1 enzyme polymorphisms, showing how they affect vitamin D receptor function, transport, and activation. Smaller studies suggest these variants may influence visceral fat and waist circumference in vitamin D-supplemented individuals, while larger studies indicate no direct effect on BMI.

4. Efficacy of Vitamin D Supplementation in Individuals with Obesity

Numerous studies consistently show that individuals with obesity not only have lower baseline serum 25(OH)D concentrations but also exhibit a reduced response to vitamin D supplementation compared with normal-weight individuals. For example, a meta-analysis by De Oliveira et al. demonstrated that the effectiveness of vitamin D supplementation is diminished in obese subjects, with increasing doses failing to produce a significant rise in serum vitamin D levels [29]. This attenuated response may be related to obesity-associated impairments in hepatic or renal function, which could affect vitamin D metabolism and bioavailability [29].

In a systematic review and meta-analysis of 94 studies, Zittermann et al. estimated vitamin D requirements according to body weight and age [30]. The authors developed a predictive equation for calculating individualized daily vitamin D doses required to achieve serum concentrations >50 or >75 nmol/L across different body weights [30]. Similarly, Drincic et al. proposed an alternative predictive model, while Van Groningen et al. developed a calculation for the loading dose of cholecalciferol required to reach a serum 25(OH)D concentration of 75 nmol/L (see Table 1 below) [31,32]. These models highlight the need for weight-adjusted or weight-based dosing strategies, particularly in individuals with overweight or obesity.

Table 1. Predictive equations for estimating the increment or required loading dose of vitamin D (authors' own summary).

Author	Predictive Equation	Example of Calculation
Zittermann et al. [30]	Incremental change in 25(OH)D (nmol/L) = 49.4 + 16.5 × $\log_{10}$[dose (IU/day)] − 0.42 × BMI	To increase 25(OH)D by 25 nmol/L (~10 ng/mL) in an individual with BMI 30, a daily dose of approximately 2000 IU is required.
Drincic et al. [31]	Vitamin D_3 dose (IU/day) = [body weight (kg) × Δ25(OH)D (ng/mL)] × 40	To increase 25(OH)D by 25 nmol/L (~10 ng/mL) in a person weighing 80 kg: 80 × 10 × 40 = 32,000 IU/week (≈4500 IU/day).
van Groningen et al. [32]	Loading dose of cholecalciferol (IU) = 40 × (75 − baseline 25(OH)D [nmol/L]) × body weight (kg)	For an individual with baseline 25(OH)D = 40 nmol/L and body weight 80 kg: 40 × (75–40) × 80 = 112,000 IU (can be divided into weekly doses).

References cited in the table are listed in the Reference section.

Ekwaru et al. analyzed 22,214 assessments of serum 25(OH)D and demonstrated an exponential dose–response relationship between oral vitamin D intake and achieved serum levels [33]. Despite relatively high baseline 25(OH)D concentrations, individuals with overweight or obesity had the lowest levels and the smallest response to supplementation. The authors concluded that obese individuals require approximately two- to threefold higher vitamin D doses, and overweight individuals about 1.5-fold higher doses, to achieve comparable serum 25(OH)D concentrations [33].

5. Vitamin D, Obesity, and Metabolic Dysregulation

The interplay between obesity, vitamin D deficiency, and metabolic syndrome (MetS) has been extensively investigated, revealing multiple interrelated pathophysiological mechanisms. Low circulating concentrations of vitamin D are consistently associated with an increased risk of MetS, type 2 diabetes mellitus (T2DM), and cardiovascular disease, with these associations being partly mediated by visceral adiposity and the endocrine–metabolic disturbances characteristic of obesity [34,35].

At the molecular level, the active form of vitamin D (calcitriol), exerts pleiotropic effects through activation of the vitamin D receptor (VDR) in key insulin-sensitive tissues, including skeletal muscle, adipose tissue, and the liver. Experimental studies demonstrate that VDR activation modulates insulin signaling pathways by regulating insulin receptor expression, activating PPARγ, promoting phosphorylation of insulin receptor substrate-1 (IRS-1), and facilitating glucose transporter type 4 (GLUT4) translocation, thereby improving insulin sensitivity and glucose utilization [36–40].

In parallel, vitamin D plays a significant role in attenuating obesity-related low-grade inflammation and oxidative stress. Calcitriol suppresses the expression of pro-inflammatory cytokines and chemokines, modulates adipokine secretion, improves mitochondrial function, and downregulates the renin–angiotensin–aldosterone system (RAAS), contributing to improved blood pressure regulation and metabolic homeostasis [41–45]. Additionally, vitamin D protects pancreatic β-cells from apoptosis and supports insulin secretion and β-cell functional capacity, further linking vitamin D status to glucose homeostasis [46–51].

Clinical and experimental evidence suggests that vitamin D supplementation may favorably influence leptin and adiponectin levels, reduce insulin resistance, and improve metabolic flexibility, particularly in individuals with overweight or obesity and low baseline 25(OH)D concentrations. Although findings from randomized controlled trials remain inconsistent—largely due to heterogeneity in baseline vitamin D status, dosing regimens, and population characteristics—available data indicate that supplementation may reduce the risk of MetS or T2DM in vitamin D-deficient individuals [1,52,53] (see Figure 3).

At the same time, adequate vitamin D status may represent a modifiable factor in the prevention and early management of obesity-related metabolic complications. Consistent with these mechanistic and clinical findings, recent Polish guidelines advocate routine screening for vitamin D deficiency in overweight or obese patients with prediabetes and recommend individualized high-dose vitamin D supplementation, adjusted for body weight and baseline 25(OH)D status, to achieve serum concentrations above 30–50 ng/mL [54].

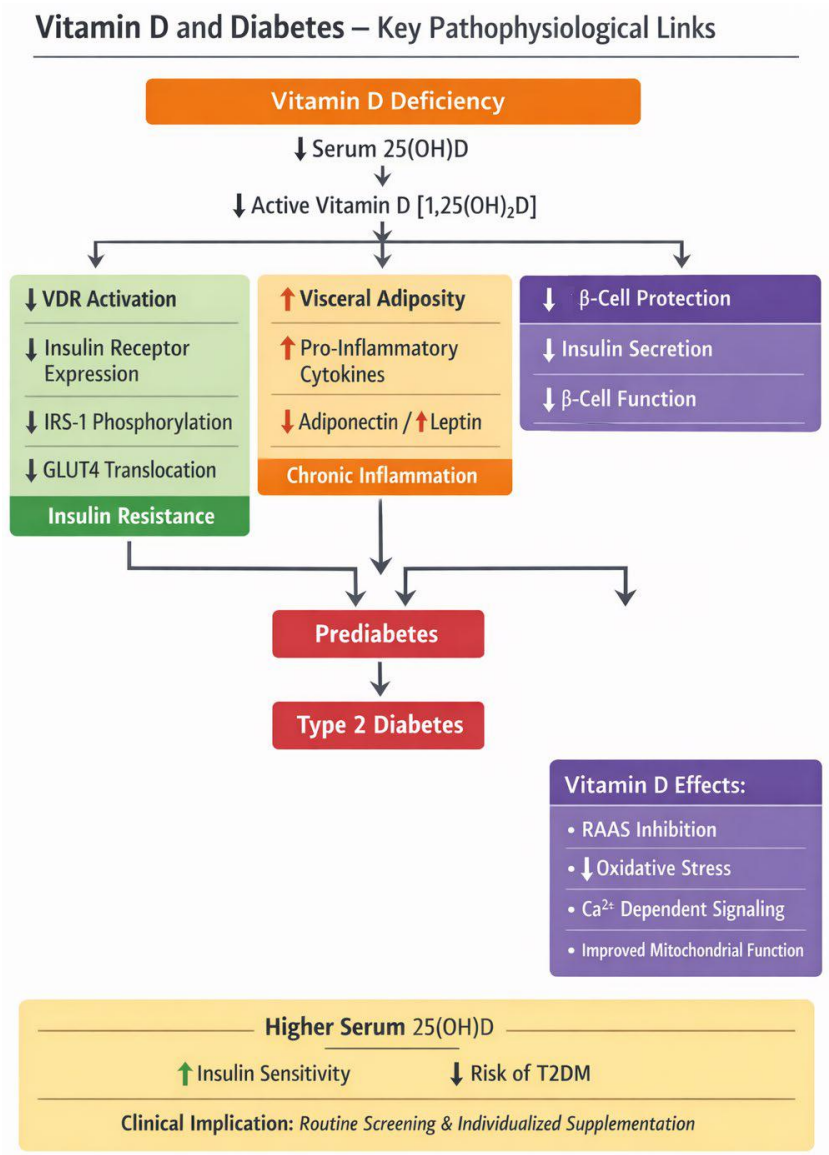

Figure 3. Vitamin D and Insulin Resistance in Obesity and Type 2 Diabetes. Schematic overview of the pathophysiological links between vitamin D deficiency and the development of insulin resistance, prediabetes, and type 2 diabetes. Vitamin D deficiency leads to the reduced activation of the vitamin D receptor (VDR), impaired insulin signaling in peripheral tissues, increased visceral adiposity and chronic low-grade inflammation, and β-cell dysfunction, thereby promoting insulin resistance and dysglycaemia. In contrast, higher serum 25(OH)D concentrations are associated with improved insulin sensitivity and a reduced risk of type 2 diabetes, supporting the clinical relevance of vitamin D status assessment and individualized supplementation.

6. Effect of Weight Reduction on Serum 25(OH)D Concentrations

If excess adiposity reduces serum 25(OH)D concentrations, then substantial weight loss—whether diet-induced or following bariatric surgery—should theoretically increase 25(OH)D levels, a finding supported by multiple studies [16,55]. Studies examining weight reduction consistently show increases in serum 25(OH)D without parallel changes in 25-hydroxylase expression in subcutaneous adipose tissue [23,56]. These findings suggest that the rise in 25(OH)D reflects a reduced distribution volume rather than increased metabolic production. For instance, a prospective analysis of a Tromsø study subgroup revealed that participants who reduced their BMI by $\geq$1 kg/m^2 over 14 years had on average, 4.5 nmol/L higher 25(OH)D levels, whereas those who gained weight exhibited a 2.5 nmol/L decrease [57]. A recent systematic review further confirmed a modest yet consistent

increase in 25(OH)D concentrations following weight loss: in 18 of 23 included studies, serum 25(OH)D levels increased post-weight reduction, although the effect size varied considerably. Meta-regression analysis showed that a 10 kg weight loss was associated with a 6 nmol/L increase in serum 25(OH)D, while a 10% reduction in fat mass was associated with a 9 nmol/L increase [55,56]. These changes appear proportional to reductions in specific adipose depots, particularly visceral fat, which contains approximately 20% more intact vitamin D than subcutaneous fat. Consequently, a greater reduction in visceral fat is therefore expected to yield a larger increase in circulating 25(OH)D [1]. In a recent intervention study involving men with visceral obesity, a 50% reduction in intra-abdominal fat volume was associated with a 26% increase in serum 25(OH)D [58]. These findings underscore that lifestyle interventions targeting visceral adiposity can produce biologically meaningful improvements in serum 25(OH)D levels and supports the concept that adipose tissue acts as a reversible storage compartment rather than a site of irreversible sequestration.

7. Can Vitamin D Influence the Development or Course of Obesity?

Although evidence from human studies remains limited, current data suggest that calcitriol production within adipose tissue is likely homeostatically regulated and not mediated by parathyroid hormone. It is also well established that calcitriol inhibits the maturation of preadipocytes, a finding mainly demonstrated in cell models, while evidence from human adipose tissue remains less consistent [59]. Therefore, although vitamin D supplementation may potentially limit further expansion of adipose tissue, its ability to reduce already accumulated fat mass appears limited [9]. Vitamin D acts directly on adipose tissue through VDR, which are expressed in adipocytes, thereby influencing local lipid metabolism. Experimental studies suggest that calcitriol may influence adipocyte metabolism by stimulating lipolysis, decreasing lipid accumulation in differentiated 3T3-L1 adipocytes, downregulating adipogenic gene expression, and upregulating lipolytic genes simultaneously [9,60]. Although obesity does not appear to alter calcium-sensing receptor expression in white adipose tissue, vitamin D has been shown to promote apoptosis of mature adipocytes through a rapid, non-genomic increase in intracellular calcium, independently of nuclear VDR signaling [61,62].

Despite these mechanistic findings, RCTs have not reported convincing effects of vitamin D supplementation on adiposity parameters in individuals with obesity. Some effects of vitamin D on body fat or body weight have been observed, particularly in trials combining vitamin D with calcium supplementation. The largest of these, the Women's Health Initiative (WHI)—a double-blind, placebo-controlled RCT involving 36,282 postmenopausal women—assessed the effects of 400 IU/day of vitamin D_3 combined with 1000 mg of calcium versus placebo. The WHI reported a modest reduction in weight gain over the seven-year supplementation period compared with placebo (mean difference −130 g). However, this effect occurred only in women with baseline calcium intake below the recommended dietary allowance (1200 mg/day); no effect was observed among participants with adequate calcium intake [63]. A meta-analysis of 12 trials (605 participants in each group) found no significant effect of vitamin D supplementation on fat mass and only a small, statistically nonsignificant difference in BMI (standardized mean difference −0.10), limited to individuals with lower baseline 25(OH)D concentrations [64]. A more recent and comprehensive analysis of 26 RCTs (each with ≥50 participants) likewise failed to show any independent beneficial effect of vitamin D on obesity or other adiposity measures. Comparisons of vitamin D versus placebo and vitamin D plus calcium versus calcium alone revealed no independent effect of vitamin D and no dose-dependent relationship between the administered amount and changes in adiposity markers [65,66]. Although current evidence does not support a direct effect of vitamin D on body weight or BMI, few studies

have examined its impact on regional fat distribution. Two parallel double-blind trials by Rosenblum et al., in which vitamin D was added to orange juice, suggested a modest reduction in visceral fat without changes in total body weight, BMI, or waist circumference; however, the concurrent calcium supplementation precludes attributing these effects to vitamin D alone [67].

8. Safety of Supplementation and Indications for Monitoring Vitamin D Levels

The serum total 25-hydroxyvitamin D [25(OH)D] concentration, comprising both $25(OH)D_3$ and $25(OH)D_2$, is widely recognized as the most reliable biomarker of vitamin D status. Most international expert bodies define optimal 25(OH)D levels as 75–125 nmol/L (30–50 ng/mL), a range primarily associated with the prevention of osteomalacia and maintenance of bone health. However, the optimal concentrations required for the so-called extraskeletal effects of vitamin D remain a subject of debate. Serum 25(OH)D concentrations vary widely in the general population, depending on season, latitude, lifestyle, skin pigmentation, body mass index, age, sex, physical activity, dietary intake, and genetic polymorphisms. Because levels typically decline in winter, maintaining slightly higher concentrations during summer may help offset this seasonal decrease. Measuring serum 25(OH)D at the end of winter or early spring maximizes the likelihood of detecting deficiency and allows timely intervention. Initially, 25(OH)D testing was indicated primarily in patients with musculoskeletal disorders. In recent years, interest in assessing vitamin D status has grown due to its potential pleiotropic effects, although their clinical relevance remains uncertain. Clinical judgment plays a key role—first identifying high-risk individuals, then confirming deficiency through laboratory assessment. Present guidelines are based on available evidence and focus on both prevention and treatment of deficiency across different age and risk groups. Interpretation of serum 25(OH)D must always consider individual factors, particularly age, body weight, and overall health status [68–71], (see Table 2).

Table 2. Clinical significance of serum 25(OH)D concentrations (authors' own summary).

Serum 25(OH)D Level	Interpretation	Clinical Significance
≤20 ng/mL (≤50 nmol/L)	Vitamin D deficiency—immediate therapeutic intervention required	Vitamin D deficiency—risk of osteomalacia, secondary hyperparathyroidism, and reduced bone mineral density
20–30 ng/mL (50–75 nmol/L)	Suboptimal status—consider increasing the dose	Insufficiency—levels at the lower end of the optimal range, possible effects on skeletal and extraskeletal functions
30–50 ng/mL (75–125 nmol/L)	Optimal status—recommended for prevention and treatment	Optimal range—target levels recommended by most expert societies
50–100 ng/mL (125–250 nmol/L)	High vitamin D intake—consider dose reduction	Potentially excessive levels—generally without clinical benefit; caution advised with long-term supplementation
>100 ng/mL (>250 nmol/L)	Risk of toxicity—discontinue supplementation immediately and monitor levels	Risk of toxicity—possible hypercalcemia, hypercalciuria, and other complications

9. Vitamin D Supplementation in Obese Patients: Current Recommendations

Obesity represents a major risk factor for the development of vitamin D deficiency, with multifactorial underlying mechanisms. According to the Endocrine Society (2024) guidelines, obesity itself is not an indication for routine 25(OH)D measurement [69]. The Endocrine Society bases its recommendations primarily on systematic reviews and meta-analyses, which have not demonstrated that screening and subsequent vitamin D supple-

mentation in obese patients improve predefined clinical outcomes [68,69]. In contrast, some national guidelines, such as the Polish recommendations (updated 2023), classify obesity as a clearly defined risk group [70,71]. In summary, while the Endocrine Society (2024) emphasizes a cautious, individualized approach, the Polish guidelines (2023) provide pragmatic and specific framework, identifying individuals with obesity as a high-risk population and recommending approximately double the standard vitamin D doses, together with a higher upper safe intake limit [70,71] (see Table 3).

Table 3. Comparison of recommendations for adult obese patients, 2023–2025 (authors' own summary).

Domain	Endocrine Society (2024) [69]	Polish Guidelines (2023; 2025 *) [54,70,71]
Screening (measurement of 25(OH)D)	Routine screening is not recommended in obese individuals without other indications (e.g., hypocalcemia, malabsorption, liver or kidney disease).	Routine population screening is not recommended, but obesity is listed among high-risk conditions—testing is advised, particularly in symptomatic patients or those with comorbidities.
Risk of deficiency	Obesity increases the risk of low 25(OH)D levels (often <50 nmol/L). Bariatric surgery further exacerbates the risk.	Obesity (especially BMI > 30, and particularly >40) is identified as a clear risk factor for vitamin D deficiency; bariatric surgery represents a specific high-risk condition requiring monitoring.
Supplementation—general	Routine supplementation solely on the basis of obesity is not recommended. Empirical supplementation may be considered in at-risk individuals.	Supplementation is explicitly recommended in obese individuals, with doses approximately twice those of the general population of the same age.
Dosage—daily intake	Standard doses (e.g., 800–2000 IU/day in adults); no specific dose escalation for obesity, though the response to supplementation is attenuated.	Adults with obesity: 2000–4000 IU/day (i.e., approximately double the standard age-specific dose). If 25(OH)D levels (30–37.5 nmol/L) initiate vitamin D therapy with 20,000 IU twice weekly or 50,000 IU once weekly; reassess serum 25(OH)D and calcium after 1 month to guide further dose adjustment. *
Upper safe limit (UL)	UL for adults: 4000 IU/day.	In obese individuals: UL increased to 10,000 IU/day (250 µg).
Monitoring	Measurement should be performed only when clinically indicated.	In obese individuals, reassessment is recommended after 1–3 months of deficiency treatment to verify achievement of optimal levels.
Form of supplement	Cholecalciferol (vitamin D_3) preferred; parenteral administration only exceptionally.	Cholecalciferol (D_3) preferred; calcifediol may be used when faster correction is required.
Clinical outcomes of supplementation	Large RCTs in obese populations have not demonstrated a clear benefit regarding fracture, CVD, or mortality reduction.	The goal is to maintain optimal serum levels (75–125 nmol/L), as deficiency is associated with higher skeletal and metabolic risk.

References cited in the table are listed in the Reference section. * is citation [54].

10. Efficacy of Vitamin D Supplementation in Obesity

Despite strong observational associations between low 25(OH)D concentrations and obesity-related metabolic disturbances, randomized controlled trials (RCTs) have not provided consistent evidence that vitamin D supplementation improves clinically relevant outcomes in individuals with obesity. Large-scale trials, including VITAL, D-HEALTH, Women's Health Initiative (WHI) and FIND, have generally failed to demonstrate significant effects of vitamin D supplementation on body weight, adiposity, insulin sensitivity, or major cardiometabolic endpoints [72–75]. These findings suggest that vitamin D supplementation in individuals with normal baseline levels may not confer additional benefit, and that a universal supplementation strategy may not be optimal.

Some subgroup analyses suggest that obese and vitamin D-deficient individuals may benefit from higher, body-weight–adjusted dosing. For example, results from the Finnish FIND study were more promising, particularly among obese participants. A higher daily

dose of vitamin D (3200 IU) was associated with a reduction in major cardiovascular events, and achieving serum 25(OH)D concentrations above 100 nmol/L was linked to a lower risk of type 2 diabetes in individuals with prediabetes [74].

A key limitation of all major RCTs lies in the relatively high baseline 25(OH)D concentrations and the inclusion of generally healthy populations. Moreover, the study populations in these trials were predominantly overweight or obese (mean BMI ~27–30 kg/m^2), and they used relatively low vitamin D doses to achieve optimal 25(OH)D levels, which may have further limited the observed effect. Clinically, supplementation should therefore be targeted primarily at individuals with low serum 25(OH)D levels, preferably administered daily rather than as large intermittent boluses, with dosage adjusted according to BMI and metabolic profile. Such an individualized approach may increase the probability of achieving meaningful clinical outcomes, which large population-based interventions have not yet demonstrated (see Table 4).

Table 4. Overview of major RCTs on Vitamin D supplementation in obese individuals (authors' own summary).

Study	Dosage/Population	Baseline 25(OH)D Level	Main Findings	Strengths	Limitations
VITAL (USA) [72]	2000 IU/day; 25,000 participants; median BMI ≈ 28	78 nmol/L	No effect on fractures (HR 1.17), CVD (HR 0.98), or malignancies (HR 1.13)	Large sample size, long-term follow-up, good adherence	High baseline 25(OH)D levels, low proportion of deficient participants, non-significant effect in obese subgroup
WHI (USA) [73]	400 IU/day + calcium; 36,000 post-menopausal women	~70 nmol/L (estimated)	No effect on mortality (HR 0.93) or fractures (HR 0.73)	Very large cohort, long-term observation	Low vitamin D dose, combined with calcium, lower adherence
FIND (Finland) [74]	1600 vs. 3200 IU/day; 2500 participants; higher BMI than in VITAL	75 nmol/L	No effect on overall mortality or malignancies (HR 0.91–1.61). In obese subgroup: reduced CVD risk (HR 0.19) and lower T2DM incidence when 25(OH)D > 100 nmol/L	Higher doses, robust design, subgroup analyses possible	Normal baseline 25(OH)D, limited generalizability to deficient populations
D-HEALTH (Australia) [75]	60,000 IU/month (≈2000 IU/day); 21,000 participants	77 nmol/L	No effect on mortality, CVD, or malignancies	Large sample size, long-term follow-up	Bolus dosing, high baseline levels, limited effect in obese individuals
Smaller RCTs/Meta-analyses [76–78]	Various doses, often in deficient populations	25–50 nmol/L	Positive effects on immunity, musculoskeletal health, and glucose metabolism in deficient individuals	Supports biological plausibility, benefits in low vitamin D status	Small sample sizes, methodological heterogeneity, shorter follow-up periods.

References cited in the table are listed in the Reference section.

11. Research Gaps and Future Directions

Although the relationship between vitamin D status, obesity, and metabolic health has been extensively studied, several important questions remain unresolved. The inconsistent results of randomized controlled trials are likely driven by substantial methodological heterogeneity, including differences in baseline 25(OH)D concentrations, supplementation regimens, achieved serum levels, intervention duration, and participant characteristics. Importantly, many large-scale RCTs enrolled individuals with sufficient vitamin D status

at baseline, which may have limited the ability to detect potential benefits in vitamin D-deficient and metabolically vulnerable populations, including individuals with obesity.

A major unresolved issue concerns the optimal biomarker for assessing vitamin D status in obesity. The relative physiological relevance of total versus free 25(OH)D, as well as the influence of vitamin D-binding protein (DBP) concentrations and genetic polymorphisms, requires further investigation. Emerging evidence suggests that alternative markers, including free and bioavailable 25(OH)D and the vitamin D metabolite ratio (VMR = 24,25$(OH)_2D_3$/25$(OH)D_3$), may provide a more accurate reflection of vitamin D status, particularly in individuals with obesity or altered DBP concentrations. The incorporation of these parameters into future studies could improve interpretation of vitamin D sufficiency and its associations with metabolic and cardiometabolic outcomes.

Mechanistic studies are also needed to better elucidate alterations in vitamin D metabolism, tissue distribution, and receptor signaling within adipose tissue, and to determine whether these changes contribute causally to insulin resistance, low-grade inflammation, or impaired energy homeostasis. Further research should address the long-term safety and efficacy of higher daily vitamin D doses in individuals with obesity, the potential role of cofactors such as calcium and magnesium, and gene–nutrient interactions influencing interindividual responsiveness to supplementation.

Finally, integrating vitamin D assessment into broader metabolic and nutritional frameworks—rather than considering supplementation as an isolated intervention—may support more clinically meaningful and personalized prevention and treatment strategies in obesity-related disorders.

12. Conclusions

Obesity represents an important risk factor for low circulating concentrations of 25-hydroxyvitamin D, reflecting a combination of increased sequestration in adipose tissue, expanded distribution volume, and altered vitamin D pharmacokinetics. Consequently, individuals with obesity commonly exhibit lower serum 25(OH)D concentrations and a reduced biochemical response to standard supplementation. Increasing evidence suggests that these findings predominantly reflect altered distribution, binding, and dilutional effects rather than a uniform functional vitamin D deficiency at the tissue level. Although low circulating 25(OH)D concentrations in obesity have been associated with disturbances in bone metabolism, insulin resistance, metabolic syndrome, and cardiovascular disease, the causal nature of these associations remains incompletely established. Emerging data on free and bioavailable vitamin D further indicate that total serum 25(OH)D may not fully reflect vitamin D availability to target tissues in obesity, although methodological heterogeneity currently limits definitive conclusions and routine clinical implementation. Future interventional studies should focus on vitamin D-deficient obese populations and use weight-adjusted dosing strategies to clarify potential clinical benefits.

Taken together, current evidence supports a cautious and individualized clinical approach. Assessment of vitamin D status and supplementation may be appropriate, particularly in the presence of established indications, skeletal involvement, or confirmed deficiency; however, routine high-dose supplementation solely on the basis of obesity is not supported by robust evidence for clinical benefit. In this context, careful interpretation of 25(OH)D concentrations is warranted, taking into account body composition, distribution volume, and clinical context rather than relying on uniform threshold-based definitions.

From both clinical and public health perspectives, prevention and effective management of obesity remain central strategies—not only for optimizing vitamin D bioavailability to target tissues, but also for improving overall metabolic health and reducing obesity-related morbidity. Addressing excess adiposity therefore represents a more fundamen-

tal intervention than vitamin D supplementation alone in mitigating the endocrine and metabolic consequences associated with obesity.

Author Contributions: J.J. wrote the main manuscript. J.K. and Z.K. critically revised and edited the manuscript. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by the project MH CZ—DRO. (General University Hospital in Prague—VFN, 00064165).

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: The data presented in this study are available on request from the corresponding author.

Conflicts of Interest: The authors declare no competing interests.

Abbreviations

25(OH)D	25-hydroxyvitamin D (calcidiol)
ATP	Adenosine triphosphate
BAT	Brown adipose tissue
BMI	Body mass index
Ca	Calcium
CKD	Chronic kidney disease
CYP24A1	Cytochrome P450 family 24 subfamily A member 1
CYP27B1	Cytochrome P450 family 27 subfamily B member 1
CYP2R1	Cytochrome P450 family 2 subfamily R member 1
VDBP	Vitamin D-binding protein
D-HEALTH	D-Health Trial (Australia)
DHCR7	7-Dehydrocholesterol reductase
FIND	Finnish Vitamin D Trial
GLUT4	Glucose transporter type 4
IU	International unit
MetS	Metabolic syndrome
PPARγ	Peroxisome proliferator-activated receptor gamma
PTH	Parathyroid hormone
RAAS	Renin–angiotensin–aldosterone system
RCTs	Randomized controlled trials
RXR	Retinoid X receptor
T2DM	Type 2 diabetes mellitus
UCP1	Uncoupling protein 1
UVB	Ultraviolet B radiation
VDR	Vitamin D receptor
VDREs	Vitamin D response elements
VITAL	Vitamin D and Omega-3 Trial
WAT	White adipose tissue
WHI	Women's Health Initiative

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