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Is vitamin D deficiency a risk factor for obesity-related morbidity, prediabetes, and type 2 diabetes — a literature review and proposals from the experts of the Polish Society of Endocrinology

Andrzej Milewicz[1], Beata Kos-Kudła[2], Marek Ruchała[3], Alicja Hubalewska-Dydejczyk[4], Dariusz Kajdaniuk[2], Bogdan Marek[2]

[1]*Department of Endocrinology, Diabetology and Isotope Therapy, Medical University of Wrocław, Wrocław, Poland*
[2]*Chair of Pathophysiology and Endocrinology, Medical University of Silesia, Katowice, Poland*
[3]*Department of Endocrinology, Metabolism and Internal Medicine, Poznań University of Medical Sciences, Poznań, Poland*
[4]*Chair and Department of Endocrinology, Jagiellonian University Medical College, Kraków, Poland*

Abstract

Through pleiotropic effects related to the presence of its receptors in major human organs, vitamin D (VD) plays an important role in systemic homeostasis, especially in the proper functioning of muscles and bones. In light of the published data from both animal and human studies, VD deficiency should be considered a risk factor for obesity-related morbidity, prediabetes, and type 2 diabetes (T2D); in addition, VD supplementation in VD deficiency has a beneficial effect on the effects of treatments aimed at normalization of body weight (including incretin drugs) and the metabolism of carbohydrates in prediabetes and T2D. The objective of this paper is to present the current knowledge and evidence on the relationship between VD deficiency and obesity, prediabetes, and T2D. The paper is intended to be used as a practical guide. The authors propose that serum 25(OH)D concentrations be determined in adults who are obese or overweight (i.e., belonging to the group presenting with a multiple increase in the risk of VD deficiency) or adults who are obese or overweight and have prediabetes or T2D. The baseline VD levels should determine the therapeutic dose and be helpful in assessing the effectiveness of therapy. The available literature lacks precise information regarding the recommended doses of VD in obese people, with 4000 IU being a frequently suggested daily dose. Most papers recommend that body weight be taken into account when determining the dose of VD in the obese; the dose should be higher than in individuals with normal body mass index (BMI). The authors suggest that in the case of low VD levels (< 20.0 ng/mL), quite frequently as low as 12.0–15.0 ng/mL, in an adult obese patient, VD therapy should be started at 20,000 IU two times per week or 50,000 IU once a week with 25(OH)D and calcium levels being checked after one month so that a decision can be made on the further course of therapy. The suggested 25(OH)D concentration target range is > 30–50 ng/mL. In a patient-tailored supplementation model, the dose of VD should depend on body weight and, most importantly, on the baseline VD level. In the absence of the expected effects, the authors suggest that the dose of VD (usually vitamin D3) be increased or the treatment be switched to calcifediol or alfacalcidol, or calcitriol in special cases such as impaired kidney or liver function. It is important to emphasize the need to individualize the management and monitor blood calcium and creatinine levels during chronic VD therapy, including high-dose therapy. **(Endokrynol Pol 2025; 76 (6): 579–585)**

Keywords: *vitamin D; obesity; type 2 diabetes; prediabetes; vitamin D deficiency; risk groups; cholecalciferol; calcifediol; alfacalcidol; calcitriol*

Introduction

Through pleiotropic effects related to the presence of its receptors in major human organs, vitamin D (VD) plays an important, well-documented role in systemic homeostasis, especially in the proper functioning of muscles and bones [1–3].

Obesity, along with the associated cardiometabolic disorders and type 2 diabetes (T2D), is among the most important public health challenges today [4, 5].

The objective of this paper is to present the current knowledge based on the bibliometric analysis tools such as HistCite, VOSviewer, and CiteSpace, and meta-analyses available from Medline (via PubMed) and Embase databases, along with the evidence regarding the relationship between obesity, prediabetes, T2D, and VD deficiency. The paper is intended to be used as a practical guide.

Is obesity related to vitamin D deficiency?

In recent years, numerous publications have highlighted the important role of VD deficiency in the etiology of obesity and its complications [6, 7]. A considerable number of *in vitro* studies have shown significant effects of VD on key adipose tissue parameters and adipocyte

Prof. Andrzej Milewicz MD, PhD, Brossa 16, 53–134 Wrocław, Poland; e-mail: andrzej.milewicz@umw.edu.pl

biology, including adipogenesis and regulation of gene expression in response to energy homeostasis and inflammation [8–10].

All this evidence underscores the role of VD in the physiology of adipose tissue, prompting a large number of studies aimed at unraveling the link between VD and obesity in both humans and animals [6]. Cross-sectional studies in humans have shown that low VD concentrations were often correlated with obesity and its parameters [11–13]. Prospective studies were indicative of low VD levels as a predictor of obesity incidence [14–16].

Genetic analyses carried out in small patient cohorts demonstrated the impact of polymorphisms in genes encoding proteins involved in VD metabolism, i.e., single nucleotide polymorphism (SNPs) within the VD receptor (VDR) and VD binding protein (VDBP) genes [17–19]. No clear results are available from studies on the effect of VD supplementation on obesity, with two meta-analyses showing no correlation and one showing improvement in obesity parameters [20–22]. The discrepancy in these observational results may be due to the lack of baseline VD levels being determined in the subjects receiving VD supplementation. Such measurements would have facilitated individualized supplementation, with the patient's body weight being taken into account, unlike in the studies in question. Daily clinical practice demonstrates the beneficial effects of VD supplementation in obese individuals when body weight and baseline VD levels are taken into account. VD supplementation is also a valuable adjunct to incretin drug therapy for obesity, through its beneficial effects on tissue insulin sensitivity.

When analyzing the reasons for the low levels of this VD in the obese, it is important to consider, among other factors, the differences in the lifestyles of obese and non-obese individuals, including the eating habits, sedentary lifestyle, and clothing habits. Lower bone mineral density was also reported in obese patients following calorie-restricted diets [23]. The key mechanism, however, appears to consist of VD sequestration, a phenomenon involving its storage in adipose tissue, which can lead to a reduction in blood concentration and a marked decrease in bioavailability (through accumulation in adipose tissue) [24].

De Oliveira et al. carried out a meta-analysis to demonstrate a reduction in the effectiveness of VD supplementation in obese subjects compared to those of normal weight, noting that increasing the doses did not significantly increase the measured VD levels [25]. This could be the result of impaired hepatic or renal function in the obese group. In such cases, a switch should be made to alfacalcidol or calcitriol (noting that calcitriol is 2× more potent than alfacalcidol). Some studies revealed associations between VDR polymorphisms and body mass index (BMI), obesity markers, or obesity [26, 27], while relationships between the BMI and the polymorphisms within the *VDBP* and *CYP27b1* genes were shown in other reports. However, no correlations between the polymorphisms in genes encoding the key factors in VD metabolism could be demonstrated in larger studies [28, 29]. Interestingly, polymorphisms within the *VDR* gene can translate to changes in visceral adipose tissue and waist circumference in VD-supplemented individuals [30]. A Mendelian randomization analysis including genes involved in VD metabolism (*VDBP*, *DHCR7*, *CYP2R1*, and *CYP24A1*) as instrumental variables suggests that low 25(OH)D concentration has little or no effect on BMI [31], that obesity promotes a decrease in plasma 25(OH) levels, and that a 1 kg increase in body weight leads to a 1.15% decrease in the 25(OH)D levels. Consistent with these findings, a systematic review and meta-analysis of randomized and non-randomized controlled trials showed that weight loss can improve plasma 25(OH)D concentrations [32]. Another meta-analysis showed that weight loss of about 10 kg with no VD supplementation can increase plasma 25(OH)D concentrations by up to 6 nmol/L [33].

There is no basis for treating VD as a weight-reduction drug. Rather, VD is one of the necessary adjuncts to obesity therapy, repairing disturbed metabolism, facilitating obesity treatment, and preventing obesity buildup.

We propose that serum VD (i.e., 25(OH)D) concentrations be determined in adults who are obese or overweight (i.e., belonging to the group with a multiple increase in the risk of VD deficiency), especially those with comorbidities. The baseline VD level is needed for two reasons: as the starting point for the determination

Table 1. ***Summary of recommendations for vitamin D (25(OH)D) use in patients with obesity, prediabetes, and type 2 diabetes (T2D)***

Recommendation	
1. Determination of 25(OH)D levels	In all patients with obesity, prediabetes, and T2D
2. Target concentration	> 50 ng/mL
3. Dose individualization	Body weight and baseline 25(OH)D blood levels to be taken into account
4. Higher doses in the obese	Frequently above the standard 2,000 IU/day; usually 4,000 IU/day or regimens of 20,000–50,000 IU per week
5. Treatment follow-up	After 4 weeks, assessment of 25(OH)D and calcium levels → dose adjustment
6. Alternative medications	Calcifediol, alfacalcidol or calcitriol in cases of renal or hepatic insufficiency

of the therapeutic dose and as the reference for the evaluation of the effectiveness of the initiated therapy, i.e., re-determination after 4 weeks of therapy.

The available literature lacks precise information regarding the recommended doses of VD in obese people, with 4000 IU being a frequently suggested daily dose. Most papers recommend that body weight be taken into account when determining the dose of VD in the obese, which should be higher than in people with a normal BMI. We suggest that in the case of very low VD levels, frequently as low as 12.0–15.0 ng/mL, in an adult obese patient, VD therapy should be started at 20,000 IU two times per week or 50,000 IU once a week with 25(OH)D and calcium levels being checked after one month so that a decision can be made on the further course of therapy.

In the absence of the expected effects, we suggest that the dose of VD (usually vitamin D_3 — cholecalciferol, less commonly vitamin D_2 — ergocalciferol) be increased or the treatment be switched to calcifediol or alfacalcidol, or calcitriol in special cases such as confirmed hepatic or renal impairment.

The lack of randomized trials with precise algorithms for VD dosing in obesity justifies the need to individualize management or monitor blood calcium and creatinine levels during chronic high-dose VD therapy.

Is maternal obesity during pregnancy a risk factor for obesity in the child?

As demonstrated by Crozier et al. in a group of 977 women, low 25(OH)D concentrations at gestation week 34 were associated with a low percentage of fat mass at birth and a high percentage of fat mass in children at 4 and 6 years of age [34]. This observation was confirmed in another study involving 922 mothers at gestation week 15, as well as in 4,903 mothers with severe VD deficiency, which was associated with a higher percentage of fat mass and a lower percentage of lean mass in children at 6 years of age [35, 36]. Other authors also demonstrated that maternal blood VD levels were inversely correlated with BMI, body weight, and waist circumference in children aged 4 and 6 years [37], as well as with high risk of fetal and neonatal overweight [38]. Only one long-term follow-up study (20 years) is available in the literature, showing no relationship between maternal obesity and concomitant VD deficiency during pregnancy and distant cardiometabolic outcomes in children [39]. Palacios et al. carried out a meta-analysis of 22 studies involving 3,725 women, aimed at finding out whether VD supplementation affects pregnancy. The researchers showed that VD supplementation during pregnancy reduced the risk of preeclampsia, gestational diabetes, and low birth weight of babies born at term [40]. The results of another meta-analysis of 11 studies involving 3,960 pregnant women showed that VD supplementation was also associated with lower BMI and BMI z-score in children aged 3–6 years [41]. The beneficial effect of VD supplementation in pregnancy is also emphasized by a recent consensus of the Endocrine Society [42].

The presented evidence supports the important role of VD deficiency in the etiology of obesity, including pregnancy, and its preventive effect on obesity. Confirming the aforementioned findings is a recent meta-analysis of more than 6,000 publications, as accomplished by Song et al., which also highlights the important role of VD in adipocyte differentiation, fat accumulation, effects on metabolism, tissue insulin sensitivity, and inflammatory processes in obesity [43].

Does vitamin D deficiency affect prediabetes?

Impaired ability of insulin to stimulate glucose uptake in peripheral tissues is one of the key pathomechanisms in prediabetes and T2D. In cell line studies, VD was shown to regulate tissue insulin sensitivity in metabolically relevant peripheral organs [45]. Initial *in vitro* studies suggested that $1,25(OH)_2D$ activates the VDR to increase the expression of insulin receptors; more recent studies showed that $1,25(OH)_2D$ activation targets peroxisome proliferator-activated receptor gamma (PPARγ), which is responsible for insulin receptor activation [46, 47]. Skeletal muscles, as an organ, play a very important role in the phenomenon of insulin resistance. Studies on myoblasts revealed that $1,25(OH)_2D$ reduces insulin resistance and increases glucose uptake through sirtuin 1 (SIRT1) activation, insulin receptor substrate 1 (IRS1) phosphorylation, and glucose transporter type 4 (GLUT4) translocation in these cells [47, 48]. As also found by Wright et al., VDR activation increases muscle calcium ions (Ca^{2+}) levels, GLUT4 translocation, and glucose uptake [49]. Zhang et al. demonstrates that VD and calcium supplementation can improve pancreatic β-cell function in prediabetic patients with low 25(OH)D levels [50]. In a cohort study, Valer-Martinez et al. observed that VD plays a role in modulating the risk of diabetes. Higher baseline VD levels may have a protective effect in preventing T2D incidents [51]. All these findings underscore the important role of VD in regulating tissue insulin sensitivity.

Within the adipose tissue of obese individuals, $1,25(OH)_2D$ reduces the expression of pro-inflammatory cytokines [interleukins (IL): IL-1β, IL-6, and tumor necrosis factor alpha (TNF-α)] [52] and chemokines: C-C

motif chemokine ligand 2 and 5 (CCL2, CCL5), C-X-C motif chemokine ligand 10 and 11 (CXCL10, CXCL11) [53] released by adipocytes and resident immune cells [54], which consequently inhibits inflammatory responses.

VDR activation was shown to affect hepatic macrophages, reducing inflammation and insulin resistance in mice with diet-induced obesity [55]. In contrast, increased hepatic resistance to insulin was observed in a study conducted in *VDR* gene knockout animals [56].

In addition, several other mechanisms have been postulated for the effect of VD deficiency on insulin resistance, including through stimulation of parathormone secretion, an increase of which reduces insulin resistance by stimulating GLUT1 and GLUT4 secretion in adipose tissue, liver, and muscle [57, 58].

In addition, VD decreases the activity of the renin-angiotensin-aldosterone axis, which results in inhibition of peripheral insulin resistance affecting pancreatic β-cell function and inhibition of GLUT4 recruitment [59, 60]. Also highlighted is the significant effect of $1,25(OH)_2D$ on the activity of the Ca^{2+}/calcium/calmodulin-dependent protein kinase kinase beta (CaMKK-beta)/AMP-activated protein kinase (AMPK) pathway and formation of reactive oxygen species (ROS), which has important implications for insulin resistance [61, 62].

Recently, numerous clinical papers have been published confirming the important role of VD deficiency in insulin resistance and as a risk factor for the development of T2D [63–66]. In a consensus statement on VD, prediabetes, and diabetes, Giustina et al. also confirmed the important role of VD deficiency in insulin resistance. A meta-analysis of data from the D2d (US), Tromso (Norway), and DPVD (Japan) trials showed that VD supplementation reduced the risk of prediabetes progressing to T2D by 15% and increased the likelihood of return to normoglycemia by 30%. Interestingly, study participants maintaining blood VD levels of 50.0 ng/mL or more presented with a 76% reduction in the risk of T2D compared to those with VD levels of 20–29.0 ng/mL [67].

In conclusion, we suggest that serum VD levels be determined in overweight or obese patients with prediabetes. If VD deficiency, or concentration below 20,0 ng/mL, is determined [44, 68], the treatment should aim at achieving the 25(OH)D level within the range of > 30–50 ng/mL [44, 67]; the recommended dose should depend on the patient's body weight and, most importantly, on the baseline VD levels [67]. We suggest a dose of 20,000 IU twice per week or 50,000 IU once a week be administered to adult patients, with 25(OH)D and calcium levels being checked after one month, so as to help in making the decision regarding the further course of therapy.

In the absence of the expected effects, we suggest that the dose of VD (usually vitamin D_3 — cholecalciferol, less commonly vitamin D_2 — ergocalciferol) be increased or the treatment be switched to calcifediol or alfacalcidol, or calcitriol in special cases such as confirmed hepatic or renal impairment.

The lack of randomized trials with precise algorithms for VD dosing in obesity justifies the need to individualize management or monitor blood calcium and creatinine levels during chronic high-dose VD therapy.

Does vitamin D deficiency affect the risk and the course of type 2 diabetes?

The current state of knowledge on the mechanisms by which VD deficiency affects carbohydrate metabolism and prediabetes has been discussed above, and therefore, this part of our position shall consist of an updated review of studies on the relationship between VD deficiency and T2D.

In their study of 1029 participants, Jorde et al. demonstrated a negative relationship between serum 25(OH)D levels and BMI during the winter months. They also demonstrated a positive relationship between 25(OH)D levels and insulin sensitivity and β-cell secretory function [69].

In an observational study spanning 29 years in more than 9,000 individuals, Afzal et al. demonstrated a close relationship between VD deficiency and the risk of T2D, with gender, age, BMI, and other health-related factors being taken into account [70].

Similar observations were also made by Song et al. in a meta-analysis of 21 prospective trials in 76,220 individuals without diabetes and in 4,996 individuals with T2D, with a correlation being demonstrated between higher levels of 25(OH)D and a lower risk of diabetes, a 10 nmol/L increase in serum 25(OH)D levels correlating with a 4% reduction in the incidence of T2D [71].

Several other studies failed to show any relationship between VD and insulin levels as well as the incidence of T2D [72, 73]; however, these studies had been conducted on small subject groups with short follow-up times.

Chen et al. carried out a meta-analysis of 39 randomized trials involving 2,982 participants to demonstrate that glycemic control depends on the dose and duration of VD supplementation, baseline VD levels, and BMI in patients with T2D. VD supplementation significantly reduced serum glucose, glycated hemoglobin (HbA_{1c}), Homeostatic Model Assessment of Insulin Resistance (HOMA-IR), and fasting insulin levels in patients with T2D. The effects were particularly pronounced when VD was administered in short-term and in high doses to VD-deficient patients who were overweight or obese,

or who had presented with baseline HbA_{1c} levels of 8% or greater. This analysis points to the validity of VD supplementation being used as an adjunct treatment for T2D [74].

Tang et al. performed a meta-analysis of 47 randomized trials involving 44,161 people without diabetes, analyzing parameters of carbohydrate metabolism over 4 months of VD supplementation at a dose of 4000 IU/day. VD supplementation significantly reduced fasting glucose levels by 0.11 mmol/L, fasting insulin levels by 1.47 mIU/L, and HOMA-IR by 0.32 while increasing total 25(OH)D concentrations to 40.14 nmol/L. The meta-analysis showed that VD supplementation can improve glucose and insulin metabolism in adults without diabetes, showing the most beneficial effects at a dose of 4000 IU/day [75].

Pittas et al. performed a meta-analysis of three randomized trials carried out in prediabetic adults treated with cholecalciferol at 20,000 IU (500 μg) per week or 4000 mIU (100 μg) per day or eldecalcitol at 0.75 μg per day versus placebo. VD supplementation reduced the risk of diabetes by 15% in adjusted analyses, with a 2-year absolute risk reduction of 3.3%. VD increased the probability of regression to normal glycemic control by 30% [prevalence ratio of 1.30, confidence interval (CI): 1.16–1.46]. There was no evidence of any difference in the rates of adverse events [nephrolithiasis: 1.17 (CI: 0.69–1.99); hypercalcemia: 2.34 (CI: 0.83–6.66); hypercalciuria: 1.65 (CI: 0.83–3.28); death: 0.85 (CI: 0.31–2.36)]. Among participants assigned to the VD-treated group maintaining the average serum 25(OH)D concentrations of at least 125 nmol/L (50 ng/mL) throughout the study as compared to those maintaining the levels of 50 to 74 nmol/L (20 to 29 ng/mL) during the follow-up period, cholecalciferol reduced the risk of diabetes by 76% [hazard ratio: 0.24 (CI: 0.16–0.36)], with a 3-year absolute risk reduction of 18.1% (CI: 11.7–24.6%) [76]. Another meta-analysis conducted on the same data confirmed the beneficial role of VD in non-obese individuals, suggesting that supplementation may promote recovery from prediabetes or return to normoglycemia [77].

Most of the previous meta-analyses evaluating the effect of VD deficiency on the onset of T2D were conducted in young individuals or those aged 50–60. An up-to-date meta-analysis was performed by Dominguez et al. to show whether VD deficiency could be the cause of T2D in prospective long-term studies in elderly patients. The authors found low 25(OH)D levels to be associated with the onset of diabetes in the elderly [78]. Also, the latest consensus of the Endocrine Society regarding VD supplementation recommends that it be pursued at a dose of 2,000 IU/day in people over 75 years of age [42].

Awaiting new research on VD, we recommend that its supplementation be pursued after prior determination of 25(OH)D blood levels in people presenting with overweight, obesity, prediabetes, and T2D, and, if vitamin deficiency is determined, undertaking personalized therapy with high doses of vitamin subject to clinical and biochemical monitoring.

Conflict of interest

Authors declare no conflict of interest.

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