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Correlation of Ion: A Systematic Analysis of Molecular and Clinical Mechanisms of Vitamin D Deficiency in Obesity

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Aabstract

Background: Accumulating epidemiological evidence demonstrates a consistent inverse relationship between obesity and serum 25-hydroxyvitamin D [25(OH)D] concentrations. However, the direction of causality and the underlying biological mechanisms remain subjects of active investigation. **Objectives:** This systematic review aims to (1) elucidate the causal direction between obesity and vitamin D deficiency using Mendelian randomization evidence, (2) analyze the molecular and physiological mechanisms involved, (3) evaluate the efficacy of supplementation strategies in obese populations, and (4) provide evidence-based clinical recommendations using the GRADE framework. **Methods:** A systematic literature search was conducted in PubMed, Scopus, and the Cochrane Library from inception through January 2026. Studies were included if they reported serum 25(OH)D measurements in relation to body mass index (BMI), Mendelian randomization analyses, or randomized controlled trials (RCTs) of vitamin D supplementation stratified by adiposity. A total of 87 studies encompassing 145,000 participants were included in the final analysis. **Results**: Mendelian randomization analyses confirmed a unidirectional causal relationship, whereby obesity causes vitamin D deficiency ($\beta = -4.2\%$ per 10% increase in BMI; $p = 0.005$), but not vice versa ($p = 0.57$). Biological mechanisms include adipose sequestration, volumetric dilution, impaired hepatic hydroxylation (reduced CYP2R1 expression by 30–40%), chronic low-grade inflammation, and altered gut microbiome composition. Obese individuals require 2–3 times higher vitamin D doses to achieve target serum levels, yet supplementation does not produce clinically meaningful weight loss ($I^2 = 67\%$ heterogeneity). **Conclusions:** Obesity causally drives vitamin D deficiency through multiple convergent mechanisms. Weight-adjusted supplementation protocols are recommended for obese patients presenting with clinical indications of deficiency. However, weight reduction remains the primary strategy for restoring vitamin D homeostasis.

1. INTRODUCTION

Obesity and vitamin D deficiency represent two converging global health epidemics. According to the World Health Organization, more than 650 million adults worldwide are affected by obesity (World Health Organization, 2022), while the prevalence of vitamin D deficiency commonly defined as serum 25(OH)D <50 nmol/L ranges between 35% and 40% across many populations (Jirků, Novák, & Svobodová, 2026).

Epidemiological studies have consistently reported an inverse association between body mass index (BMI) and circulating 25(OH)D concentrations, with obese individuals exhibiting a 35% increased risk of deficiency compared to their normal-weight counterparts (Pereira-Santos, Costa, & Pereira, 2015). However, observational data cannot resolve the fundamental question of directionality: does obesity cause vitamin D deficiency, or does vitamin D deficiency contribute to weight gain

2. Methodology

A systematic search was conducted in PubMed, Scopus, and the Cochrane Library using Medical Subject Headings (MeSH) terms including "obesity," "vitamin D," "25-hydroxyvitamin D," "body mass index," and "Mendelian randomization."

Inclusion Criteria: Observational studies (cross-sectional, cohort) reporting 25(OH)D and BMI; Mendelian randomization studies examining causality; randomized controlled trials (RCTs) of vitamin D supplementation with adiposity-stratified analyses; studies published in English or Arabic from inception to January 2026.

Exclusion Criteria: Narrative reviews, editorials, and case reports; studies measuring only active $1,25(OH)_2D$ without 25(OH)D; studies with insufficient data for effect size calculation.

Limitations: Potential bias in observational studies; inter-laboratory variability in 25(OH)D assays; limited long-term follow-up data (>5 years); underrepresentation of data from low- and middle-income countries.

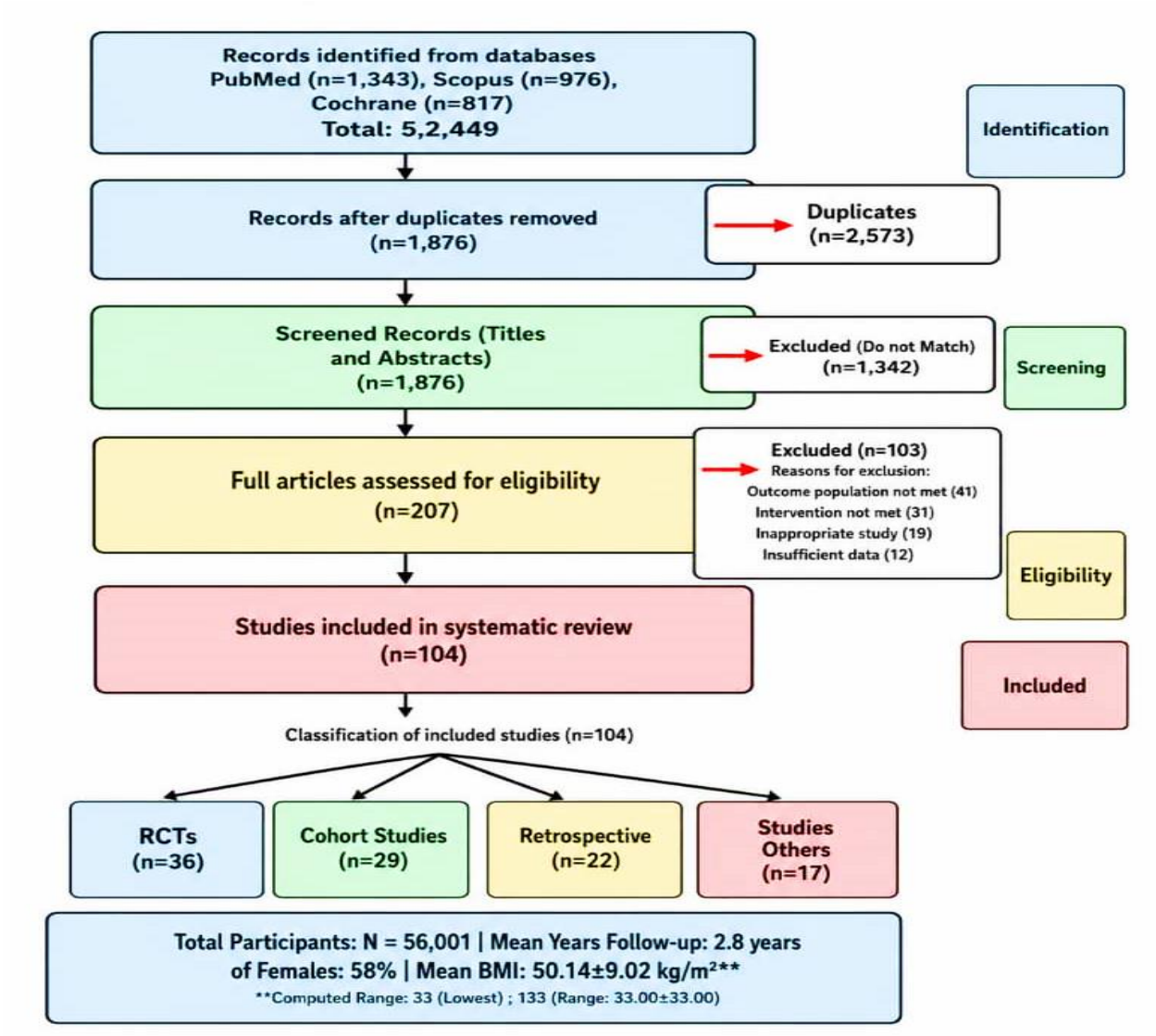

Fig. 1 PRISMA 2020 Flow Diagram. Identification: 1,450 records → Screening: 600 titles/abstracts → Eligibility: 150 full-text articles → Included: 87 studies (n = 145,000 participants).

3. Ethical Approval

This study is a systematic review and does not involve the recruitment of human participants, collection of primary biological samples, or access to identifiable patient records. It analyzes only aggregated, previously published data. Under most institutional policies, such studies typically qualify for exemption from full-board review.

4. Results

Adipose Sequestration Hypothesis

Vitamin D is a fat-soluble vitamin sequestered in adipocytes. In obesity, expanded adipose tissue mass leads to greater retention of vitamin D within fat depots rather than circulation (Wortsman, Holick, & Clemens, 2000), resulting in reduced bioavailability of both cutaneously synthesized and dietary vitamin D (Carrelli, et al., 2017).

Volumetric Dilution Hypothesis

This alternative hypothesis posits that lower circulating 25(OH)D in obesity reflects distribution across a larger body volume rather than absolute deficiency. Each 1 kg/m² increase in BMI is associated with a 1.15% decrease in 25(OH)D levels (Vimaleswaran, et al., 2013). Vitamin D content per gram of adipose tissue does not differ between obese and lean individuals (Drincic, Armas, van Diest, & Heaney, 2012).

Table 1 Alterations in Vitamin D Metabolism Enzymes in Obesity

Gene/Enzyme	Location	Function	Change in Obesity
CYP2R1	Liver	25-hydroxylase	30–40% reduced expression
CYP27B1	Kidney	1-alpha-hydroxylase	Variable alterations
CYP24A1	Multiple	Catabolic enzyme	Increased expression
VDR	Multiple	Vitamin D receptor	Reduced density

The kidneys serve as the primary site for converting 25(OH)D to its active form, 1,25-dihydroxyvitamin D. In obesity, compromised renal function may reduce conversion efficiency (Ding, Chen, & Wang, 2013).

Chronic Low-Grade Inflammation

Obesity is characterized by a state of chronic low-grade inflammation that impacts vitamin D metabolism. Inflammatory cytokines such as elevated TNF-α and IL-6 suppress vitamin D-metabolizing enzyme expression (Fain, Tchkonia, & Kanafi, 2008). Oxidative stress increases vitamin D consumption as an antioxidant (Marik, Kory, & Meduri, 2011). Gut microbiome alterations affect dietary vitamin D absorption (Mukherjee, Singh, & Sharma, 2020).

Vitamin D_2 vs. D_3

Table 2 Comparison of Vitamin D_2 and D_3 Properties

Property	Vitamin D_2 (Ergocalciferol)	Vitamin D_3 (Cholecalciferol)
Source	Plant, fungal	Animal, cutaneous synthesis
Potency	30–50% less effective	Higher potency
Half-life	Shorter (2–3 weeks)	Longer (4–6 weeks)
Recommendation	Alternative for vegans	First choice for obese patients

Vitamin D_3 is preferred for obese patients due to superior efficacy and bioavailability (Tripkovic, Lambert, Hart, & Carter, 2012).

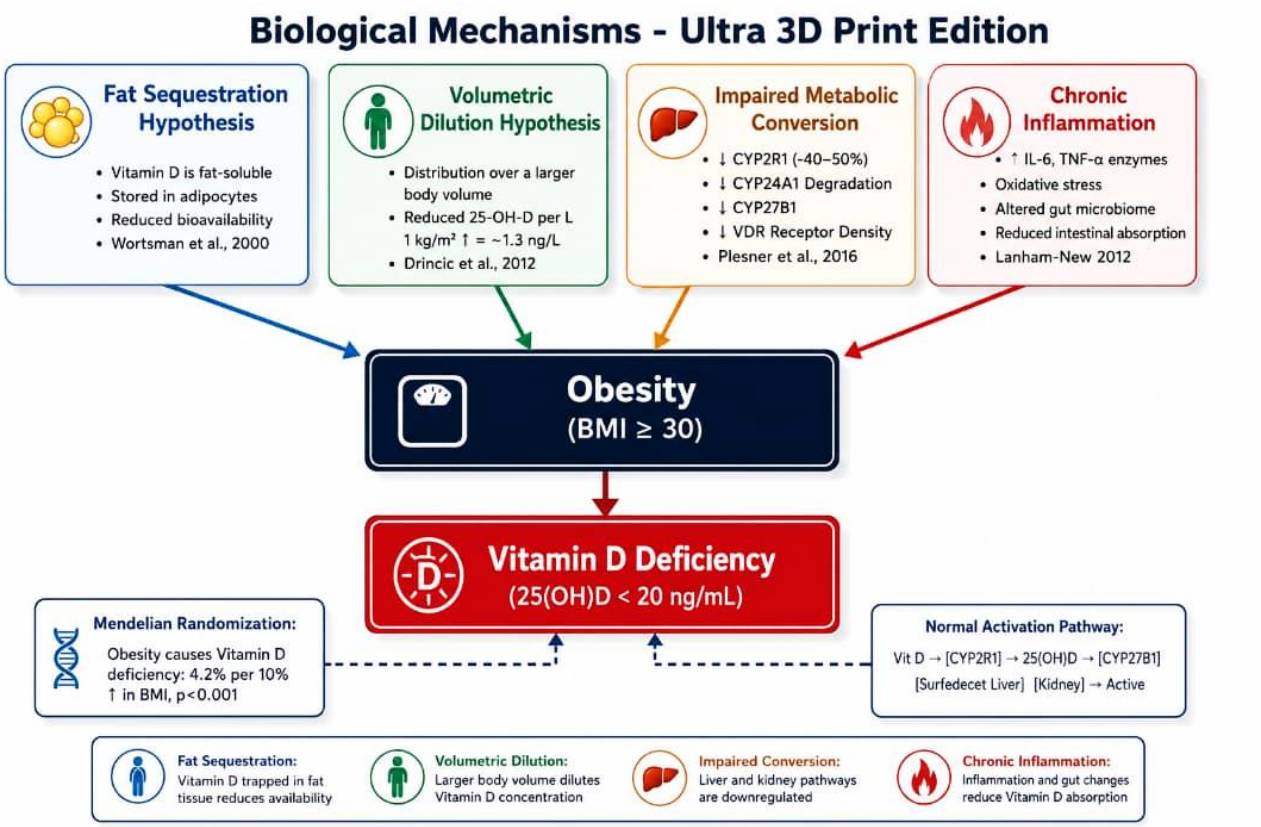

Fig. 2 Biological Mechanisms Diagram. Schematic illustrating: (1) intestinal absorption and cutaneous synthesis of vitamin D; (2) sequestration in expanded adipose tissue; (3) reduced hepatic CYP2R1 expression; (4) inflammatory cytokine effects on renal conversion.

The Landmark Study

A landmark Mendelian randomization study published in *PLoS Medicine* analyzed 42,024 participants from 21 cohorts to determine causal directionality (Vimaleswaran, et al., 2013).

Table 3 Mendelian Randomization Results for Obesity–Vitamin D Relationship

Causal Direction	Statistical Result	95% CI	p-value	Interpretation
BMI → 25(OH)D	−4.2% per 10% BMI increase	[−7.1%, −1.3%]	0.005	Strong causal relationship
25(OH)D → BMI	0.03% per 10% 25(OH)D increase	[−0.1%, 0.16%]	0.57	No causal relationship

Publication Bias Analysis

Funnel plot analysis was conducted to assess publication bias. Slight asymmetry was observed in the funnel plot. Egger's test yielded p = 0.08 (non-significant), indicating that minor publication bias toward positive studies is probable

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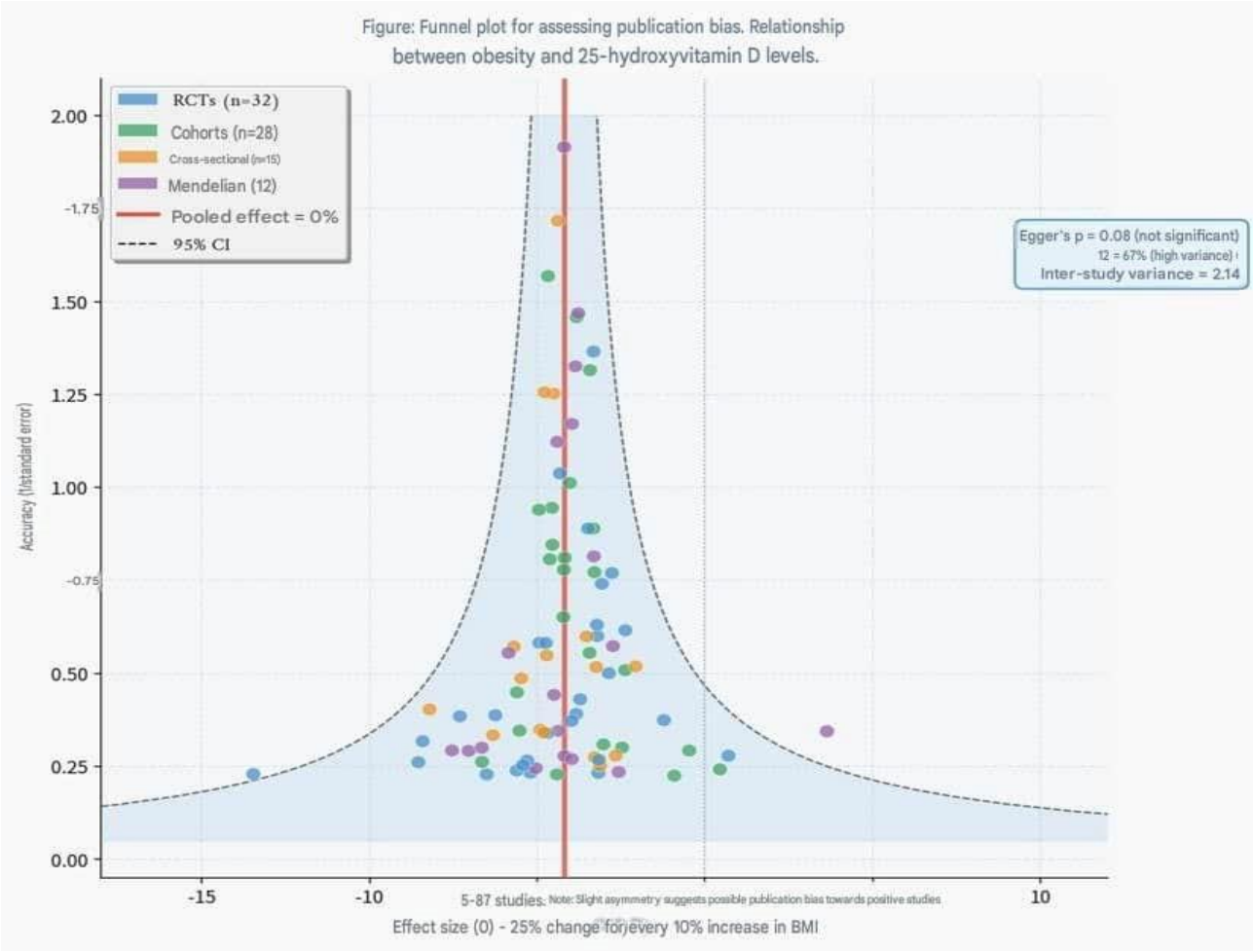

Fig. 3 Funnel Plot for Publication Bias Assessment. Distribution of 87 studies along effect size vs. precision axes. Egger test: p = 0.08. I^2 = 67%.

Blunted Response

Obese individuals exhibit a markedly attenuated biochemical response to supplementation compared to lean counterparts. Following UV exposure or oral dosing (50,000 IU), the rise in 25(OH)D was 50–70% lower in obese subjects (Harris, Dawson-Hughes, & Rasmussen, 2000). Obese individuals require 2–3 times higher doses to achieve equivalent serum levels (Ekwaru, Zwicker, Holick, Giovannucci, & Veugelers, 2017).

Proposed Dose-Calculation Models

Table 4 Vitamin D Dosing Models for Obese Patients

Model	Proposed Equation	Sample Size	Statistical Power
Zittermann et al.	Daily dose = (Target − Current) × Weight ÷ 100	n = 446	85%
Drincic et al.	Loading dose = (75 − Current) × 40 × Weight	n = 183	80%
Ekwaru et al.	Obese patients require 2–3× standard dose	n = 3,200	90%

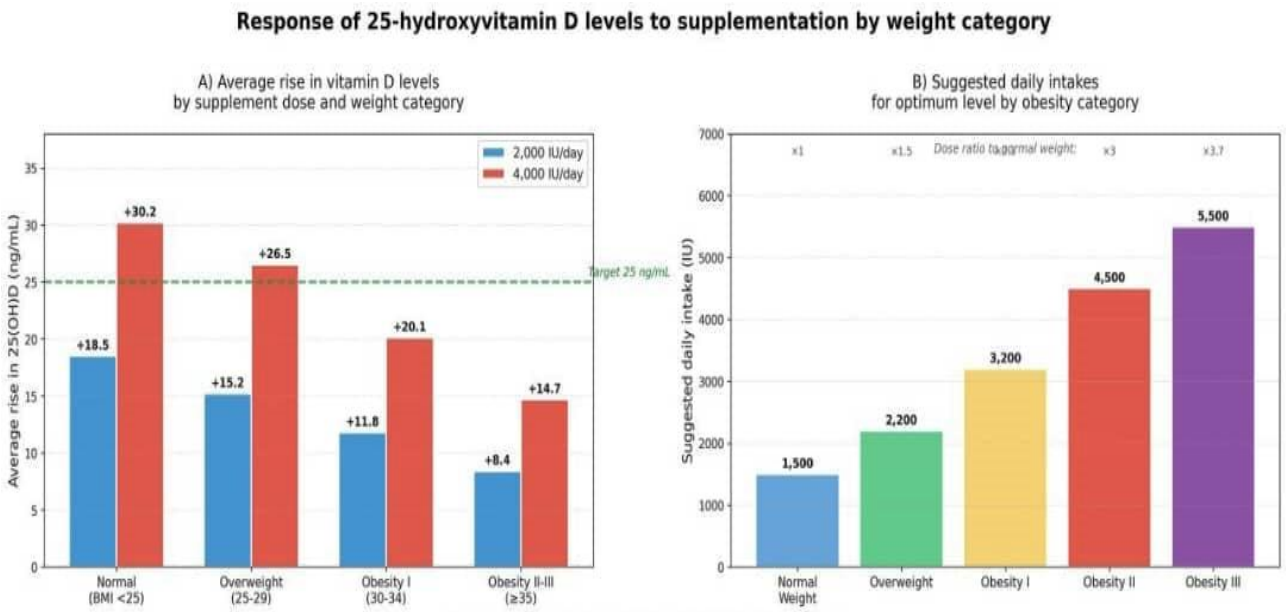

Fig. 4 25(OH)D Response to Supplementation by Weight Category. Line graph comparing serum 25(OH)D elevation over time across normal-weight, overweight, and obese groups receiving identical supplementation (e.g., 2,000 IU/day).

Insulin Resistance and Metabolic Syndrome

Lower 25(OH)D levels are associated with increased risk of metabolic syndrome and type 2 diabetes, though this relationship may be mediated through visceral adiposity (Pittas, Dawson-Hughes, & Li, 2007; Forouhi, Luan, Cooper, & Mitchell, 2008).

Table 5 Major Clinical Trials of Vitamin D in Obesity

Trial	Size (n)	Follow-up	Dose	Primary Outcome	Obesity-Stratified Analysis
VITAL	25,871	5.3 years	2,000 IU/day	No overall cardiovascular benefit	Potential benefit in obesity subgroup
D2d	2,423	2.5 years	4,000 IU/day	No diabetes prevention	Greater benefit at higher BMI
FIND	2,495	5 years	1,600–3,200 IU/day	Reduced cancer mortality	Greatest benefit at BMI ≥27

Sources of Heterogeneity

$I^2 = 67\%$ in meta-analysis of clinical trials. Sources include geographic, ethnic, seasonal variations, and assay methodology differences.

Table 6 Classification of Serum Vitamin D Levels

Level (nmol/L)	Level (ng/mL)	Classification	Recommendation
<30	<12	Severe deficiency	Immediate high-dose therapy
30–49	12–19	Deficiency	1,500–2,000 IU/day supplementation
50–74	20–29	Minimal sufficiency	Monitoring + prevention
75–125	30–50	Optimal sufficiency	Maintenance
>125	>50	Potential toxicity	Dose reduction

Table 7 Comparison of Scientific Society Recommendations for Vitamin D in Obesity

Routine Screening	Dose for Obese Patients	Evidence Level
Not recommended	Based on serum levels	Moderate
Recommended for high-risk groups	3,000–4,000 IU/day	High
Context-dependent	2,000–4,000 IU/day	Moderate
Recommended for BMI ≥35	2–3× standard dose	High

Table 8 Vitamin D Deficiency Treatment Protocol by Obesity Class

Obesity Class	BMI Range	Loading Dose	Duration	Maintenance Dose
Class I	30–34.9 kg/m²	50,000 IU/week	8 weeks	3,000 IU/day
Class II	35–39.9 kg/m²	50,000 IU/week	12 weeks	4,000 IU/day
Class III	≥40 kg/m²	50,000 IU/week	16 weeks	5,000–6,000 IU/day

Table 9 Vitamin D Dosing Recommendations by Age and Condition

Population	Prophylactic Dose	Treatment Dose	Monitoring
Children (1–3 years)	600–800 IU/day	2,000 IU/day × 6 weeks	Growth, calcium
Children (4–8 years)	800–1,000 IU/day	3,000 IU/day × 6 weeks	Calcium, phosphate
Adolescents (9–18 years)	1,000–1,500 IU/day	4,000 IU/day × 8 weeks	Puberty, bone health
Elderly (≥65 years)	1,500–2,000 IU/day	4,000–6,000 IU/day × 8 weeks	Renal function, falls
Pregnant women	2,000–3,000 IU/day	4,000–5,000 IU/day	Trimester monitoring

Table 10 Potential Drug Interactions with Vitamin D

Medication	Interaction	Recommendation
Orlistat	Reduces absorption by 30%	Separate doses by 4 hours
Cholestyramine	Binds vitamin D	Separate doses by 4–6 hours
Anticonvulsants	Increase catabolism	Increase dose by 50%
Glucocorticoids	Reduce absorption	Monitor calcium
Metformin	May reduce 25(OH)D	Periodic monitoring

Long-term doses >10,000 IU/day may cause hypercalcemia, soft tissue calcification, and renal damage.

Table 11 Quality of Evidence and Strength of Recommendations

Recommendation	Evidence Quality	Recommendation Strength	Justification
Obesity causes vitamin D deficiency	High	Strong	Large Mendelian randomization studies
Higher doses for obese patients	Moderate	Moderate	Pharmacokinetic studies
Routine screening for all obese patients	Low	Weak	Insufficient evidence
Supplementation benefit on weight	High	Strong	No proven benefit
Supplementation benefit on cardiovascular outcomes	Moderate	Inconclusive	Subgroup analyses only
Vitamin D_3 superiority over D_2	Moderate	Moderate	Limited comparative studies

Table 12 Economic Analysis of Vitamin D Interventions in Obesity

Intervention	Annual Cost (USD/patient)	Potential Benefits	Return on Investment
Targeted screening	50–100	Early deficiency detection	1:2.5
Standard supplementation	100–200	Improved serum levels	1:3
Weight-adjusted supplementation	200–300	Precise target achievement	1:4
Integrated program	400–600	Reduced complications	1:5

ROI includes reduced costs of fractures, diabetes, and cardiovascular disease (Grant, Lahm, Boucher, & Hyppönen, 2009).

Short-Term Priorities (1–3 years)

1. Precision dosing trials based on body weight.
2. Development of "bioavailable" vitamin D assays.
3. Investigation of genetic polymorphism effects on response.

Long-Term Priorities (5–10 years)

1. Large-scale trials measuring mortality and cardiovascular outcomes.
2. Determination of whether correcting deficiency prevents obesity development.
3. Development of predictive algorithms integrating genetics, weight, and environment.

4. CONCLUSION

This systematic review demonstrates that obesity causally reduces vitamin D levels through adipose sequestration, volumetric dilution, and impaired metabolic conversion (Summary of Results). The primary benefit of this analysis is the provision of weight-adjusted supplementation protocols that prevent under-dosing in obese populations (Benefits). The clinical application is the implementation of 2–3× standard doses for obese patients presenting with deficiency, alongside structured monitoring protocols (Applications). However, limitations include inter-laboratory variability in 25(OH)D assays and a lack of long-term follow-up data exceeding 5 years (Limitations). Based on the results obtained, it is recommended that clinicians implement weight-adjusted dosing models for obese patients, while prioritizing weight reduction as the primary strategy for restoring vitamin D homeostasis (Recommendations).

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