

**Review Article****Evaluating the Impact of Vitamin D Supplementation on Serum Leptin Levels: A Meta-Analysis of Randomized Controlled Trials**Bahareh Nikooyeh¹, Mohammad Esmail Motlagh², Tirang Neyestani^{1*}

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ABSTRACT

Background and Objectives: Vitamin D, crucial for bone health and calcium homeostasis, also impacts metabolic processes and endocrine functions. It may influence leptin, a key hormone regulating energy balance. This meta-analysis evaluates the effect of vitamin D supplementation on serum leptin concentrations, addressing inconsistencies and exploring its potential role in metabolic health.

Materials and Methods: This review examined supplementation with vitamin D, alone or with calcium, as an intervention for its effects on serum leptin concentrations. Following PRISMA guidelines, a comprehensive search of electronic databases up to March 2024 identified eligible trials. Eleven randomized clinical trials were included, assessing vitamin D supplementation versus placebo or control. The meta-analysis, registered in PROSPERO (www.crd.york.ac.uk/PROSPERO/CRD42020177472), used STATA for statistical analysis, with outcomes reported as mean differences (MD) and 95% confidence intervals (CIs).

Results: Initially, 503 studies were identified, with 366 excluded after screening. Ultimately, 11 studies with 819 participants were included. Trials varied in vitamin D dosage, frequency, and whether calcium was included. Pooled analysis found no significant effect of vitamin D on leptin concentrations (MD: -0.13, 95% CI -1.12 to 0.87). Subgroup analyses showed no differences based on intervention duration or calcium inclusion.

Conclusions: Our meta-analysis demonstrated that vitamin D supplementation does not significantly affect serum leptin levels, adding to the existing evidence on vitamin D metabolic roles. Further research is crucial to unravel the interaction between vitamin D and adipokines like leptin, given widespread vitamin D deficiency and its metabolic implications.

Keywords: Vitamin D, Leptin, Meta-analysis

Highlights

- Vitamin D supplementation does not have a statistically significant effect on leptin concentrations.
- Subgroup analyses did not reveal any significant differences in leptin response.
- Sensitivity analyses confirmed the stability of our primary findings.
- Vitamin D supplementation alone may not be sufficient to modulate leptin levels in diverse populations.

Introduction

Vitamin D, a fat-soluble vitamin essential for maintaining bone health and calcium homeostasis, has garnered significant interest for its broader physiological roles, including its impact on metabolic processes and endocrine functions (1). Recent studies have highlighted

the potential influence of vitamin D on adipokines, such as leptin, which plays a crucial role in regulating energy balance, appetite, and body weight (2-4).

Leptin, primarily produced by adipocytes, serves as a key hormone in the feedback mechanism between adipose

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tissue and the hypothalamus to modulate food intake and energy expenditure. Elevated serum leptin levels are often associated with obesity and metabolic disorders, underscoring the importance of understanding factors that can modulate leptin secretion and action (5).

Emerging evidence suggests that vitamin D may influence leptin production and secretion (2, 3). Mechanistic studies have proposed that vitamin D receptors (VDR) and the vitamin D metabolic pathway enzymes are present in adipose tissue, indicating a direct role of vitamin D in adipocyte function and leptin regulation. Furthermore, observational studies have reported correlations between vitamin D status and leptin levels, prompting further investigation into whether vitamin D supplementation can effectively alter serum leptin concentrations (6).

Despite these promising findings, the relationship between vitamin D supplementation and leptin levels remains inadequately explored and controversial. Some clinical trials have demonstrated a significant reduction in serum leptin concentrations following vitamin D supplementation, while others have reported no significant effects (7, 8). These inconsistencies highlight the need for well-designed studies to elucidate the potential benefits and mechanisms of vitamin D supplementation in leptin modulation.

Therefore, this meta-analysis aims to evaluate the effect of vitamin D supplementation on serum leptin concentrations. By addressing this gap in the literature, we hope to provide insights into the potential role of vitamin D in metabolic health and its implications for obesity and related metabolic disorders.

Materials and Methods

Description of the intervention

The intervention examined in this review was vitamin D as a single ingredient or with calcium. No limit was placed on the dose, type of intervention (supplement/fortification) or frequency at which vitamin D is taken.

This meta-analysis was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

The protocol of present study was registered in the PROSPERO International Prospective Register of Systematic Reviews (www.crd.york.ac.uk/PROSPERO/ CRD42020177472).

Research strategy

A comprehensive search of electronic databases was conducted for eligible trials up to March 2024. The following databases were covered: National Library of Medicine (PubMed), Scopus, Web of Science (WoS), and Cochrane Database of Systematic Reviews (Cochrane

Library, CDSR) using the following search terms in titles and abstracts: (vitamin D OR cholecalciferol OR ergocalciferol) AND (leptin). All of the studies were limited to English language and studies in humans

Types of studies: Inclusion and exclusion criteria

Two investigators separately searched and reviewed articles for eligibility via the following inclusion criteria: (1) all studies had to be a randomized clinical trial design (2) data description was mean \pm SD and sufficient information on leptin concentrations at baseline and at the end of follow-up in each group or providing the net change values (3) investigation of effect of vitamin D with or without calcium on serum/plasma concentrations of leptin,

Studies were excluded based on the following criteria: data being incomplete; duplicate publication of articles; obscurely reported outcomes, or lack of control groups; and animal studies, non-interventional studies.

Types of interventions and outcome measures

We evaluated the effect of vitamin D with or without calcium versus placebo, no intervention, or another dose of vitamin D (less than 400IU).

Outcome measures were serum/plasma leptin.

Data extraction and management

Two review authors independently screened titles or abstracts to exclude studies which failed to meet the mentioned criteria and then obtained the full-text reports for further assessment. Discrepancies were resolved through consensus. Detailed data on study design, context, participants' information, interventions, outcomes were extracted.

For multi-armed studies, pairs of arms relevant to the review were compared. Data for the control group were used for each intervention group comparison. The weight assigned to the control group was reduced by dividing the control group number (N) by the number of intervention groups.

The selection process in sufficient detail to complete a PRISMA flow diagram was recorded in the Figure 1 and table 1,2.

Assessment of risk of bias in included studies

Criteria for the assessment of study quality were the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (9) according to following: Random sequence generation, Allocation concealment, Blinding of participants, personnel and outcome assessment, Incomplete outcome data, selective outcome reporting and other bias (bias due to problems not covered elsewhere, e.g. industry funding).

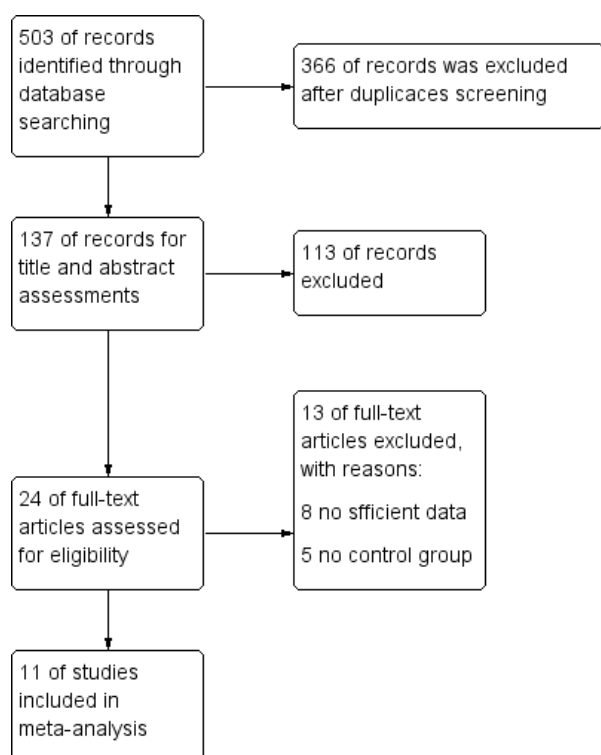


Figure 1. The protocol flowchart of the study on the effects of vitamin D intake on serum leptin concentration

Subgroup analysis and investigation of heterogeneity

If we had identified substantial heterogeneity, and there was sufficient data, we planned to investigate it using subgroup analyses and sensitivity analyses,

The following subgroup analyses were carried out:

- Duration of intervention
- Participants with or without comorbidities (for example, diabetes)
- With or without calcium

Sensitivity analysis

If there had been sufficient data to allow for sensitivity analyses, this analysis would have been performed for examining the effects on results by excluding:

- Trials at high risk of bias, as specified in the 'Assessment of risk of bias in included studies' section.
- Trials with small sample sizes (less than 15 participants in each group);

Statistical analysis

Meta-analysis was performed using STATA version 18.0 (StataCorp, College Station, TX). We did not report any dichotomous data. For continuous outcomes, a mean difference (MD) and 95% CIs calculated for each study (i.e. intervention group minus control group differences).

In addition, heterogeneity was assessed using Q test and I^2 test. The fixed effect model was used when there was no statistically significant heterogeneity ($P > 0.1$ and $I^2 < 50\%$), whereas a random-effects model was employed on the contrary ($p < 0.1$ or $I^2 > 50\%$).

Results

Description of studies

Initially 503 studies were found in a preliminary search from which 479 studies were excluded after removing duplicates and primary screening of titles and abstracts, another 24 studies were excluded for following reasons: 1) No control group; 3) The studies provided no available data. Finally, a total of 11 studies involving 819 participants were selected for the analysis (Figure 1).

For a detailed description of studies, see the tables 1,2 "Characteristics of the studies selected for analysis" and "Demographic characteristics and baseline parameters of the studies selected for analysis".

Participants

Five studies included patients with diabetes (10-14). Three trials included only participants with hypovitaminosis D (15-17) and one of them only recruited postmenopausal women (16). Likewise of five studies in overweight and obese subjects (15-19), one included only adolescents (18).

Table 1. characteristics of the studies selected for analysis.

Study	Location	Inclusion criteria	Type and dose of vitamin D	duration	Sample size
Mousa, 2020	Australia	BMI ≥ 25 kg/m ² and 25-hydroxyvitamin D (25(OH)D) ≤ 50 nmol/L	100,000 IU single bolus followed by 4,000 IU daily	16 week	Intervention: 28 Control: 26
Harreiter, 2022	European-wide multicentre	obese pregnant women	1600 IU/day	35–37 weeks	Intervention: 77 Control: 67
Mai, 2017	Italy	obese patients, serum 25(OH)D < 20 ng/mL	an oral dose of commercially available oily solution containing 600,000 IU of cholecalciferol or an equivalent volume of certified	1 month	Intervention: 12 Control: 12

Study	Location	Inclusion criteria	Type and dose of vitamin D	duration	Sample size
			cholecalciferol-free olive oil		
Duggan, 2015	USA	postmenopausal, overweight or obese (BMI \geq 25 kg/m ²), not taking hormonal therapy, with insufficient serum 25(OH)D concentrations (i.e. \geq 10 to $<$ 32 ng/mL),	2000 IU/day of oral vitamin D3 supplementation + a lifestyle based weight-loss program; or a daily placebo+ a life-style based weight-loss program	12 months	Intervention: 109 Control: 109
Belenchia et al. 2013	USA	Obese adolescent patients aged between 9 and 19 yrs and at least at the 85th percentile for BMI	2 \times 2000 IU vitamin D3 pills/day	6 months	Intervention: 18 Control: 17
Breslavsky et al. 2013	Israel	Patients with type 2 diabetes mellitus recruited from the hypertension outpatient clinic	1000 IU vitamin D3 capsules/day	12 months	Intervention: 24 Control: 23
Maggi et al. 2013	Italy	Patients who were 60 yrs or older with type 2 diabetes mellitus and diabetic foot complications	A single dose of 300,000 IU vitamin D3	6 months	Intervention: 14 Control: 16
Ghavamzadeh et al. 2014	Iran	Type 2 diabetic patients on glucose lowering agents, – but not insulin- not suffering from other illnesses (such as cardiovascular diseases, renal failure, and/or inflammatory diseases) non supplemented with vitamin D and/or Ca	Vitamin D3 (cholecalciferol) 400 IU/ml (10 mcg/ml) plus thin vegetable oil (purified component of coconut and palm oil)	3.5 months	Intervention: 26 Control: 25
Chai et al. 2012	USA	Adults aged 30–75 yrs, in general health, with a history of at least one pathology-confirmed adenomatous colorectal polyp within the past 36 months, no contraindications to calcium or vitamin D supplementation or rectal biopsy procedures and no medical conditions, habits, or medication usage that would otherwise interfere with the study	800 IU vitamin D3	6 months	Intervention: 23 Control: 23
Tabesh et al. 2014	Iran	Nonsmoker individuals aged older than 30 years with type 2 diabetes	1000 mg calcium carbonate per day vs 50 000 IU vitamin D3 per week, vs 50 000 IU vitamin D3 per week plus 1000 mg calcium carbonate per day vs and placebo	2 months	Intervention: 30, 30 Placebo: 30 Group 2, 3, 4 were included
Hajimohammadi et al, 2017	Iran	(1) fasting blood glucose $>$ 126 mg/dL, (2) willingness to participate in the study, (3) BMI between 25 and 35 kg/m ² , (4) aged 30–60 years old, (5) no intake of any supplements (including vitamins, calcium and fish oil) and herbal medicine at least 3 months to and during the intervention time	fortified yogurt drink (FD) (containing 500 IU vitamin D in each 250 cc bottle, twice a day) or plain yogurt	3 months	Intervention: 50 Control: 50

Table 2. Demographic characteristics and baseline parameters of the studies selected for analysis.

Study	Age (year)	Male (%)	BMI (kg/m ²)	25(OH)D, ng/mL
Mousa, 2020	Intervention: 31.5 ± 8.1 Control: 32.0±9.9	Intervention: 61 Control: 69	Intervention: 31.5 ± 4.8 Control: 30.3±3.8	Intervention: 12.5 ± 5.0 Control: 13.6±4
Harreiter, 2022	Intervention: 32.8 ± 5.4 Control: 32.2±5.2	0	Intervention: 33.7 ± 4.3 Control: 33.3±4.3	Intervention: 27.7 ± 10.7 Control: 26.6±10.7
Mai, 2017	Intervention: 38 ± 8.3 Control: 37±10.3	Intervention: 50 Control: 58.3	Intervention: 42.7±4.5 Control: 39.8±3.1	Intervention: 14.2±6.5 Control: 14.5±6.5
Duggan, 2015	Intervention: 60.3±5.3 Control: 59.0±4.7	-	Intervention: 32.3±5.5 Control: 32.5±6.1	Intervention: 21.4±6.2 Control: 21.4±6.1
Belenchia et al. 2013	Intervention: 14.6±2.3 Control: 13.9±2.4	Intervention: 52 Control: 48	Intervention: 39.5±5.1 Control: 38.9±6.7	Intervention: 19.2±6.3 Control: 19.6±7.9
Breslavsky et al. 2013	Intervention: 66.8±9.2 Control: 65.8±9.7	Intervention: 45.8 Control: 47.8	Intervention: 27.9±5.2 Control: 30.6±5.1	Intervention: 11.8±10.9 Control: 11.7±6.5
Maggi et al. 2013	69	Intervention: 64.2 Control: 87.5	29	Intervention: 11.2±4.4 Control: 13.6±6.9
Ghavamzadeh et al. 2014	Intervention: 52.2±10.7 Control: 49.3±10	41.1	Intervention: 28.9±4.0 Control: 27.9±4.5	Intervention: 11.2±9.9 Control: 21.4±23
Chai et al. 2012	Intervention: 60.2±38.8 Control: 62.1±35.9	Intervention: 70 Control: 70	Intervention: 28.9±26.8 Control: 31.6±28.7	Intervention: 17.2±21.5 Control: 19.4±9.1
Tabesh et al, 2014	Intervention: group 2=50.2±6.6 Group 3= 49.8±6.1, Placebo: 51±6.1	Intervention: group 2= 48 Group 3= 50 Placebo: 53	-	Intervention: group 2=11.2±5.6, group 3= 12.2±6.6 Placebo: 18.3±6.6
Hajimohammadi et al, 2017	Intervention: 52.4±8.4 Control: 52.6±6.3	Intervention: 38 Control: 48	Intervention: 28.6±4.0 Control: 30.0±4.2	Intervention: 15.4±8.0 Control: 15.2±9.1

Intervention and control groups

The trials assessed single (11, 15), daily (10, 12, 13, 16, 18, 20) or weekly (14) doses. The dose of daily vitamin D ranged from 400 IU (13) to 4000 IU (18). One study used vitamin D via fortified yogurt drink (12). All trials comparing vitamin D versus placebo or control. Two trials were multi-armed studies assessed vitamin D with or without calcium versus placebo (14, 20).

Risk of bias in included studies

The results of the assessment of the methodological quality of included trials are shown in Figure 2

Allocation

Three trials described an adequate method of generating a truly random allocation sequence (11, 18, 21). The other trials were described as "randomized", however, did not report how the random sequences were generated.

Incomplete outcome data

Three studies had loss to follow-up > 20% overall, between groups or within a group (10, 13, 18).

Other potential sources of bias

All studies clearly defined the inclusion and exclusion criteria had not a significant difference in baseline values between intervention and control groups.

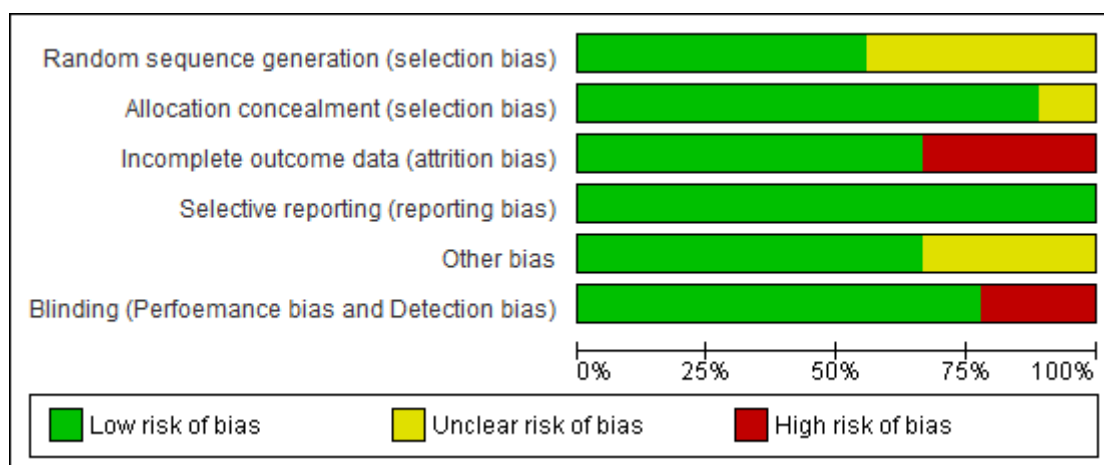


Figure 2. 'Risk of bias' graph: review authors' judgments about each risk of bias item presented as percentages across all included studies

Effects of interventions

Leptin concentrations

eleven trials compared vitamin D with or without calcium versus control. From two studies two pairs of arms relevant to the review were compared. Pooled data comparing vitamin D with or without calcium with control showed no statistically significant effect on leptin concentrations (819 participants, MD: -0.13, 95% CI -1.12 to 0.87) (Figure 3).

Subgroup analysis

We examined subgroups to look for possible differences between studies in terms of the duration of the

intervention; diabetes status at baseline; alone or combination with calcium.

There was no statistical evidence that the response of blood leptin to supplementation differed by duration of the intervention (less than 6 months vs. six months and more, p-value: 0.52)

Most of the trials provided vitamin D alone, but when two trials used vitamin D with calcium, there was no clear statistical evidence that they produced different results on leptin concentrations from those observed with vitamin D alone (p-value: 0.26).

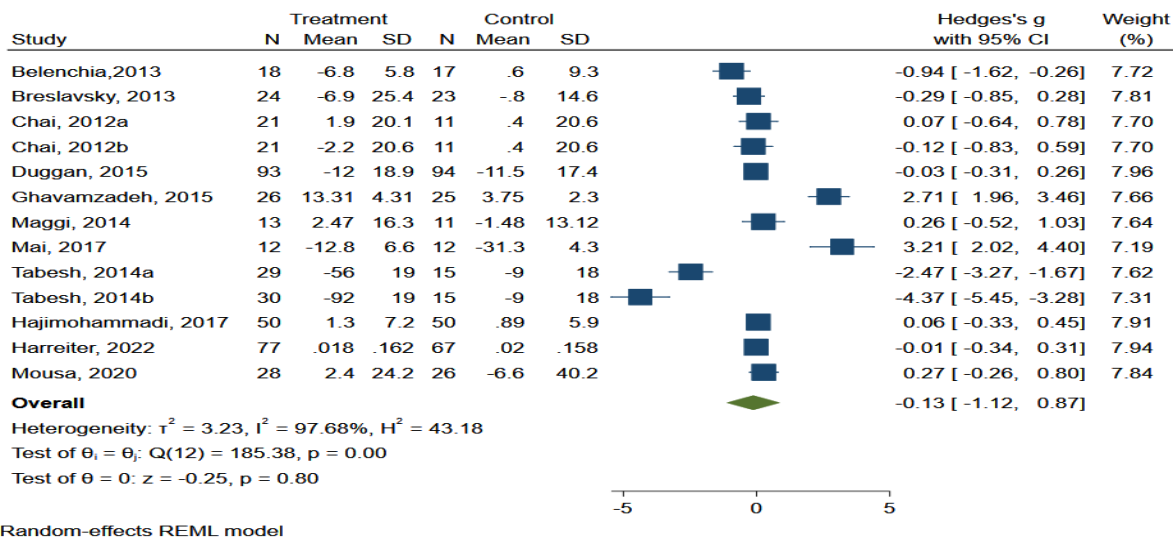


Figure 3. The treatment effect of vitamin D with and without calcium on blood levels of leptin

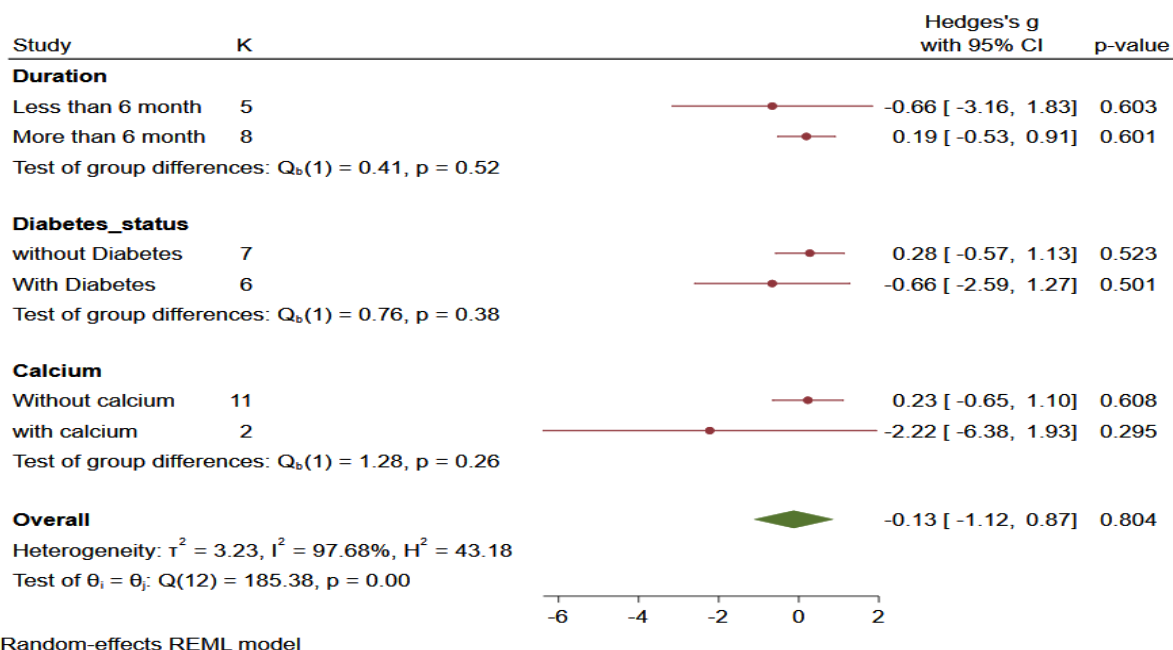


Figure 4. The subgroup analysis of effect of vitamin D on blood levels of leptin by diabetes status, duration of trials and calcium intake

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Sensitivity analysis

We carried out sensitivity analyses excluding trials with high levels of sample attrition (> 20%) and at high risk of attrition bias. We found that results were consistent with the main analyses for blood leptin levels (MD: -13.5, 95% CI -36.8 to 9.92).

Excluding the trials that included small sample size (less than 15) in each arm indicated no change in the overall results (MD: -14.8, 95% CI, -34.4 to 4.73).

Discussion

Our meta-analysis aimed to elucidate the effect of vitamin D supplementation on serum leptin concentrations by pooling data from 11 randomized controlled trials (RCTs) involving a total of 819 participants. The results indicate that vitamin D supplementation, either alone or in combination with calcium, does not have a statistically significant effect on leptin concentrations. The primary analysis, which included all 11 trials, revealed no significant changes in serum leptin levels with vitamin D supplementation compared to control (MD: -0.13, 95% CI -1.12 to 0.87). This finding was consistent across various subgroups and sensitivity analyses, suggesting a robust result that is not significantly influenced by study duration, baseline diabetes status, or the addition of calcium to the intervention.

Adipose tissue serves as a target for vitamin D and is the primary storage site for vitamin D and its metabolites (22). Leptin exerts autocrine and paracrine lipolytic effects on adipocytes by interacting with the vitamin D receptor, and it inhibits the enzyme responsible for converting 25(OH)D to 1,25-dihydroxyvitamin D. Consequently, vitamin D depletion may enhance appetite and contribute to obesity by directly regulating leptin expression (23).

Studies using in vivo and ex vivo animal models have demonstrated that 1,25(OH)₂ D₃ directly enhances leptin production in adipose tissue through a VDR-dependent mechanism. Conversely, in vitro studies on human adipose tissue have shown that vitamin D treatment inhibits leptin secretion (24). Human studies further reveal inconsistent findings regarding the relationship between vitamin D and leptin levels. Randomized controlled trials (RCTs) have similarly yielded mixed results, with some indicating that vitamin D supplementation increases leptin concentrations, others suggesting a decrease, and yet others finding no significant effect on leptin levels in overweight or obese individuals (8, 25).

Our findings are consistent with several previous studies that have reported mixed or null effects of vitamin D on leptin levels. For example, some trials included in our analysis demonstrated an increase or decrease in leptin concentrations, while others showed no effect, mirroring the heterogeneity observed in the literature (15, 20, 26).

This variability might be attributed to differences in study populations, baseline vitamin D levels, dosages, and durations of supplementation.

Subgroup analyses did not reveal any significant differences in leptin response based on the duration of intervention or the presence of diabetes. Additionally, the inclusion of calcium did not alter the effect of vitamin D on leptin levels. Sensitivity analyses excluding studies with high attrition rates or small sample sizes confirmed the stability of our primary findings, indicating that our results are robust and not significantly influenced by these factors.

Our meta-analysis has several limitations. First, the heterogeneity among included studies in terms of population characteristics, vitamin D dosages, and treatment durations could introduce variability in the results. Second, some studies did not adequately describe their randomization methods, which might affect the reliability of their findings. Third, the presence of high attrition rates in some studies could bias the results, although our sensitivity analyses suggest that this did not significantly affect the overall conclusions.

The lack of a significant effect of vitamin D on leptin concentrations suggests that vitamin D supplementation alone may not be sufficient to modulate leptin levels in diverse populations. Future research should focus on well-designed RCTs with standardized dosing regimens and clearly defined populations to further explore this relationship. Additionally, mechanistic studies are needed to elucidate the pathways through which vitamin D may influence leptin production and secretion.

Conclusion

In summary, our meta-analysis indicates that vitamin D supplementation does not have a significant effect on serum leptin concentrations. These findings contribute to the growing body of evidence on the metabolic roles of vitamin D and underscore the need for further research to fully understand the interaction between vitamin D and adipokines such as leptin. Given the high prevalence of vitamin D deficiency and the potential metabolic implications, understanding these interactions remains a critical area of study.

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Nothing to declare

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