

Effects of Vitamin D Supplementation on Adipocytokine Levels in Patients with Abnormal Glucose Metabolism: Systematic Review and Meta-Analysis of Randomized Controlled Trials



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Abstract

Objective: The objective of this systematic review and meta-analysis was to investigate the effects of vitamin D supplementation on circulating levels of adipocytokines in prediabetic and diabetic individuals

Materials and Methods: The following databases were searched from randomized controlled trials: PubMed, Medline, Scopus, EMBASE, Web of Science, Google Scholar, Cochrane Trial Register, WHO Clinical Trial Registry Platform and Clinicaltrial.gov Registry until December 2017. We assessed pooled effects of interventions as mean difference by applying the random effects model. The Cochrane Collaboration's tool was used to investigate the risk of bias. To exclude that the overall effect sizes depended on individual studies, we conducted sensitivity analysis through the leave-one-out method. We also inspected for publication bias.

Results: Our meta-analysis included 16 studies with 1058 individuals. Supplementing vitamin D significantly reduced levels of IL-6 (MD: 1.67pg/ml (95% CI-2.53, -0.80), $p=0.0002$, $I^2=99\%$), and the effects remained after sensitivity analysis. Levels of adiponectin, leptin and tumor necrosis factor-alpha (TNF-alpha) were not significantly changed. Overall study heterogeneity was high. We could not exclude publication bias.

Conclusion: Vitamin D supplementation can reduce levels of IL-6 in prediabetic and diabetic individuals, but does not affect other adipocytokines. However, a cautious interpretation of our results is warranted.

Keywords: Diabetes Mellitus; Adipokines; Vitamin D

Introduction

Diabetes mellitus is increasing at alarming rates worldwide. This condition is associated with serious health consequences and an enormous socioeconomic burden. According to recent estimates, the number of individuals suffering from diabetes rose from 108 million in 1980 to 422 million in 2014, i.e. a 4-fold increase. Somewhat higher increases have been observed in men as compared to women (4.3% to 9.0% and 5.0% to 7.9%, respectively) [1]. The economic implications of managing diabetes are enormous [2]. For instance, in the US alone, the cost of diagnosed diabetes amounted to 245 billion USD in 2012 [3]. Diabetes is associated with significant mortality, and affected individuals have a higher risk of all-cause mortality compared to non-diseased individuals [4]. The increasing prevalence of diabetes noted in the past decades goes hand in hand with the ever growing number of overweight and obese individuals. High prevalence of overweight and obesity globally along with low levels of physical activity are associated with significant part of

the world's diabetes burden [5]. According to the World Health Organization, more than 1.9 billion adults were overweight in 2014, out of which 600 million were obese [6].

The vast majority of individuals living with diabetes develop metabolic abnormalities, such as insulin resistance before developing full-blown disease. These metabolic disturbances, apparent as impaired fasting glucose and impaired glucose tolerance, collectively known as pre-diabetes, are present potentially in as up to 70% of individuals who eventually develop true diabetes [7]. Insulin resistance is the key pathological characteristic of abnormal glucose metabolism [8]. Over an observational period of 3-5 years, approximately one out of four individuals with prediabetes progresses to develop overt diabetes, but long-term most prediabetic individuals are likely to become diabetic [9]. The exact molecular mechanisms that lead from prediabetes to frank diabetes are not clear [10]. Pancreatic beta-cell failure is believed to represent the crucial step in this

process [11], and occurs within a short time period [12-14]. Changes in glucose concentration, insulin sensitivity and insulin secretion are mostly subtle in prediabetic individuals, and can go on for more than 10 years, followed by a sharp deterioration of glucose metabolism and diabetes development within 2 years [14].

Background

Body mass index [15] and body fat levels [16] are both strong predictors of insulin resistance. Other anthropometric indicators, such as waist circumference and waist/hip ratio, which are indicative of central adiposity, are also associated with the incidence of diabetes [17]. Clearly, a common denominating factor of the vast majority of prediabetic and diabetic individuals is adiposity. A paradigm shift has been brought about in the past decades as to the physiological role of adipose tissue. As large number of compounds secreted from the adipose tissue has been identified, it is now well-established that adipose tissue functions as a highly functional endocrine organ [18]. More than 600 bioactive compounds which are secreted from the adipose tissue have been identified so far [19].

Adipocytokines play a pivotal role in the main hallmark of abnormal glucose metabolism, i.e. insulin resistance [20-26], but they appear to play a major role in diabetes-associated beta-cell failure as well [27]. Indeed, dysregulated adipocytokine profile has been linked with increased incidence of diabetes in prospective studies [27,28]. The importance of adipose tissue function in susceptibility to develop diabetes becomes apparent when normal weight diabetic individuals are accounted for [29], as in this group of patients dysregulated adipocytokine profile is of great importance [30]. In addition, adipocytokines can explain a great part of comorbidities typically occurring in patients with abnormal glucose metabolism. They are suggested to be at the metabolic cross-roads connecting insulin resistance and atherosclerosis [31]. This is particularly important, as cardiovascular disease is the most common cause of death in diabetic individuals [32,33]. Furthermore, they are associated with microvascular complications in diabetic individuals [34,35], and consequently diabetic nephropathy [36-39] and retinopathy [39], with emerging evidence as to their role in diabetic neuropathy as well [40-41]. Vitamin D is a fat-soluble vitamin with a plethora of physiological functions in the body [42,43]. Globally, inadequate vitamin D levels are widely present, bearing serious health implications [44]. Given its profound metabolic effects, the significance of vitamin D in diabetes has been extensively discussed [45-47]. Although there is evidence that vitamin D deficiency is associated with a higher risk for diabetes and that maintaining adequate levels seems to exert a protective effect [48-51], there are mixed results as to the effects of vitamin D on glycemic parameters in prediabetic [52-55] and diabetic individuals [56-59], with emerging importance with respect to common diabetic complications [60-66].

Vitamin D has important physiological signalling roles in the adipose tissue [67-69], but its receptors have also been identified in infiltrating immune cells [70,71]. Correlations between vitamin D and adipocytokine concentrations such as leptin [72,73], adiponectin [73,74] and interleukin-6 [75] have already been reported, but less is clear about the effects in individuals with disturbances in glucose metabolism specifically. Recent results from the Jackson Heart Study demonstrated that the associations between vitamin D status and risk factors for cardiovascular disease are partially mediated through circulating adipocytokines [76]. Importantly, vitamin D as a fat-soluble molecule accumulates in the fat mass in obese individuals [77], so that is plausible that its effects on secretion of adipocytokines from adipose tissue might be observed particularly in this group. In light of this compelling evidence, the aim of this systematic review and meta-analysis was to investigate the effects of vitamin D on plasma adipocytokine concentrations in individuals suffering with prediabetes and type 2 diabetes, as these effects may be of clinical relevance.

Methodology

Literature Search

A systematic literature search of randomized controlled trials was conducted in the following electronic databases: PubMed, Medline, EMBASE, Scopus, Web of Science, Google Scholar, Cochrane Trial Register, WHO Clinical Trial Registry Platform and Clinicaltrial.gov Registry. No language restrictions were applied in the search. The literature was searched from inception to December 2017. We used the following search words, among others: vitamin D, cholecalciferol, calcitriol, diabetes, prediabetes, adipokines, adipocytokines. Retrieved articles were hand searched in the parts introduction, discussion and reference list to identify additional potentially relevant trials. Additionally, we also searched retrieved reviews and meta-analyses for any potentially overlooked article.

Inclusion Criteria

Any randomised controlled trial which fulfilled the following criteria was included in the analysis:

- a) Intervention involving supplementation with vitamin D or its analogues (calcidiol, ergocalciferol, cholecalciferol) regardless of the route of administration (oral, intramuscular)
- b) Parallel or cross-over design
- c) Involving adult (minimum 18 years of age) human subjects with insulin resistance, impaired glucose tolerance, impaired fasting glucose, or type 2 diabetes
- d) An intervention period with a minimum duration of 4 weeks
- e) Included an assessment of an outcome of interest, i.e. plasma concentrations of one or more adipocytokines

f) Reported post-intervention mean values or change from baseline values with standard deviation. The included studies had to be original research (not a review or conference abstract)

Risk of Bias Assessment

The Cochrane Collaboration's tool for assessing the risk of bias in randomized trials was applied to evaluate the risk of bias of the studies included in the meta-analysis by determining either low, unclear or high risk of bias to the following study characteristics: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias) [78].

Data Extraction and Analysis

Relevant variables which were predetermined from each included trial were collected independently by both authors, including sample size, sex distribution (expressed as % female participants), age, BMI, study duration and design, clinical condition and medication, vitamin D intervention (daily dose, vitamin D chemical form, route of administration), comparison group and outcomes. Data was independently extracted by the two authors.

Group means and corresponding standard deviations (SD) were extracted for the intervention and comparison group from every trial. In the case that the trial reported medians or interquartile ranges, we calculated the mean values and standard deviations [79]. Where standard error of the mean (SEM) reported instead, we calculated the SD on the basis of the following formula: $SD = SEM \times \text{square root}(n)$, where n is the number of subjects in the group. When logarithmically transformed data were reported, we used formulas suggested by Higgins [80], to calculate raw data.

Changes in serum concentrations of adipocytokines were the primary outcome for our meta-analysis and were extracted as change from baseline. Where change was not reported, we calculated it as the difference between the arithmetic means post intervention - baseline [81]. SD of mean differences were calculated as $SD = \text{square root} [(SD_{\text{baseline}})^2 + (SD_{\text{end of treatment}})^2 - (2 \times SD_{\text{baseline}} \times SD_{\text{end of treatment}})]$ for each group, assuming that $r=0.5$ [82].

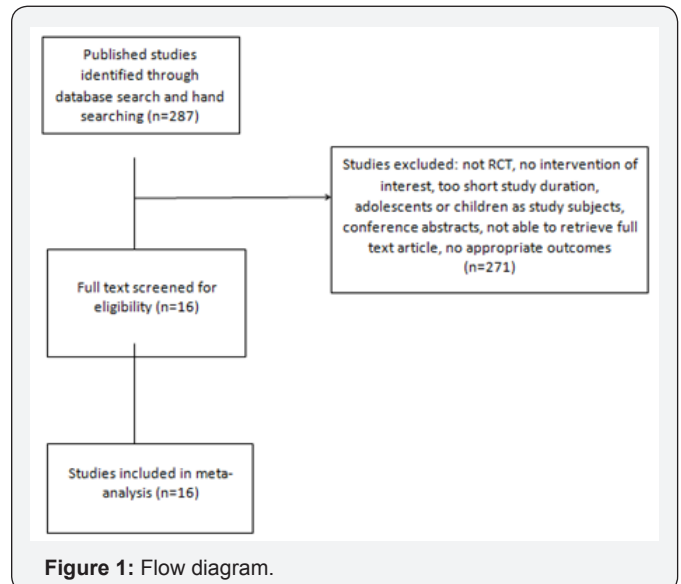
We used the software Review Manager 5.3 as provided by the Cochrane Collaboration for all statistical analysis [83]. The inverse-variance, random effects model was applied to compare post-mean values [84].

Heterogeneity was assessed by χ^2 and I^2 . An I^2 -value of greater than 50% was taken to represent considerable heterogeneity between the analyzed trials and significance was set at $p < 0.05$. In the case that a considerably different effect size was found in any one study, a sensitivity analysis was performed

through the leave-one-out method to confirm that the overall effect size was not driven by any single study. To inspect for publication bias, a funnel plot of the data (mean changes against the corresponding standard errors) was applied.

Results

Literature Search, Study Selection and Study Characteristics



Using the above described search strategy, a total of 287 studies were identified. After deduplication and applying the selection criteria, a total of 16 studies were included. Figure 1 provides a detailed overview of study selection flow. The full text was screened for quantitative data availability and all screened 16 studies [85-101] were included in the final analysis, with 1058 subjects altogether. All studies used a mixed population of males and females; two did not report sex distribution of participants [96,101]. According to the BMI, the study populations were either overweight (25-30 kg/m²) or obese (30-35 kg/m²). A total of 4 studies enrolled individuals with prediabetes [90,91,98,101] all other studies involved type 2 diabetic patients. The study duration ranged between 8 weeks and 6 months, whereas Duta 90 reported a significantly longer follow-up when compared to other studies included in the analysis.

Only one study 100 used paracalcitol and another study 85 calcitriol as supplement. Otherwise, cholecalciferol (vitamin D³) was used, out of which in 11 studies as oral supplement (in 1 study as a single bolus dose) and in 3 studies in form of fortified dough. In most studies, vitamin D was used as a sole supplement; however, in 3 studies [90,91,93] participants received calcium alongside vitamin D. Outcomes identified were concentrations of adiponectin, leptin, TNF-alpha and IL-6.

Figure 2a provides an overview of risk of bias distribution according to the above described characteristics, Figure 2b shows risk of bias assessment across individual studies. Overall,

the studies were of low or unclear risk of bias; high risk of bias was only identified in a small percentage in three study characteristics (random sequence, blinding of participants and personnel, incomplete outcome data).



Figure 2: Risk of bias assessment. Each bias domain was evaluated carefully from every trial and decided whether the information provided reflected a low risk of bias (green), high risk of bias (red), or if insufficient information was provided and the risk of bias was therefore unclear (yellow). (A) Summary of risk of bias according to characteristics. The results were pooled from every trial, combined and general results expressed as percentages. (B) Risk of bias in individual trials.

Influence of Vitamin D Supplementation on Adipocytokine Levels (Quantitative Analysis)

The current meta-analysis of 8 RCTs suggests no effects of vitamin D supplementation on circulating levels of adiponectin, as shown in Figure 3 (MD: 0.00µg/ml (95% CI -0.00, 0.00), p=0.25, I2=73%). With regards to effects on leptin (Figure 4a), pooled effect size from 5 RCT found a non-significant increase in serum concentration with vitamin D supplementation (MD: 0.82 ng/ml (95% CI -4.34, 5.98), p=0.76, I2= 40%). The magnitude of the

effect augmented after removing Tabesh [99] from the analysis (MD: 1.73 ng/ml (95% CI -3.30, 6.75), p=0.50, I2=38%) (Figure 4b). However, a non-significant reduction in leptin levels was seen once we removed Ghavamzadeh 92 from the analysis, and this also significantly reduced study inconsistency (MD= -0.09 ng/ml (95% CI -2.99, 2.82), p=0.95, I2=3%) (Figure 4c). Taken overall, it is inconclusive whether vitamin D supplementation affects circulating leptin levels.

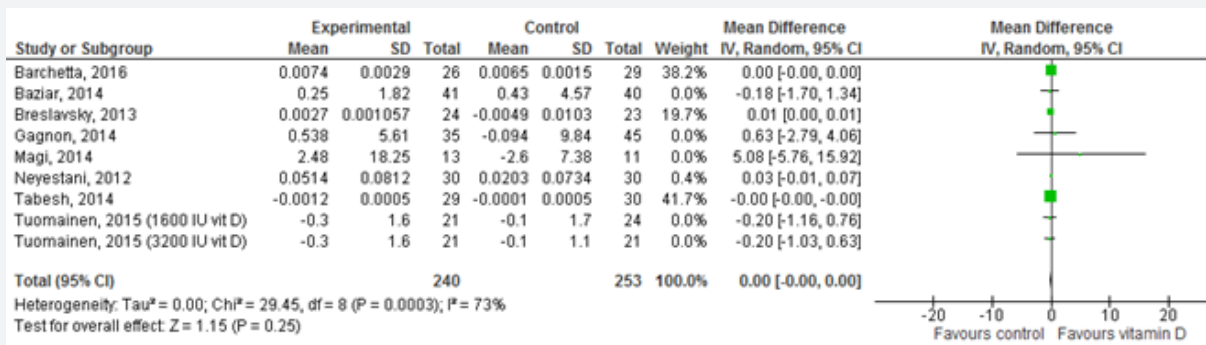


Figure 3: Effects of vitamin D supplementation on adiponectin levels (µg/ml). Forest plot shows pooled mean differences with 95% confidence intervals (CI) for 10 pooled effect sizes from 9 randomized controlled trials (two separate effect sizes were pooled for two different dosing regimens of vitamin D in Toumainen [101]). The green colored square represents the point estimate of the effect of the intervention for each trial. The horizontal line joins the upper and lower limits of the 95% CI of the effects. The square area represents the relative weight of the trial in the meta-analysis. The black colored diamond at the bottom represents the pooled mean difference with 95% CI for all study groups, but in this meta-analysis, its absent because there are no effects. Notice the labelling of the X-axis is different as compared to other outcomes, because an increase in adiponectin levels would be seen as favourable.

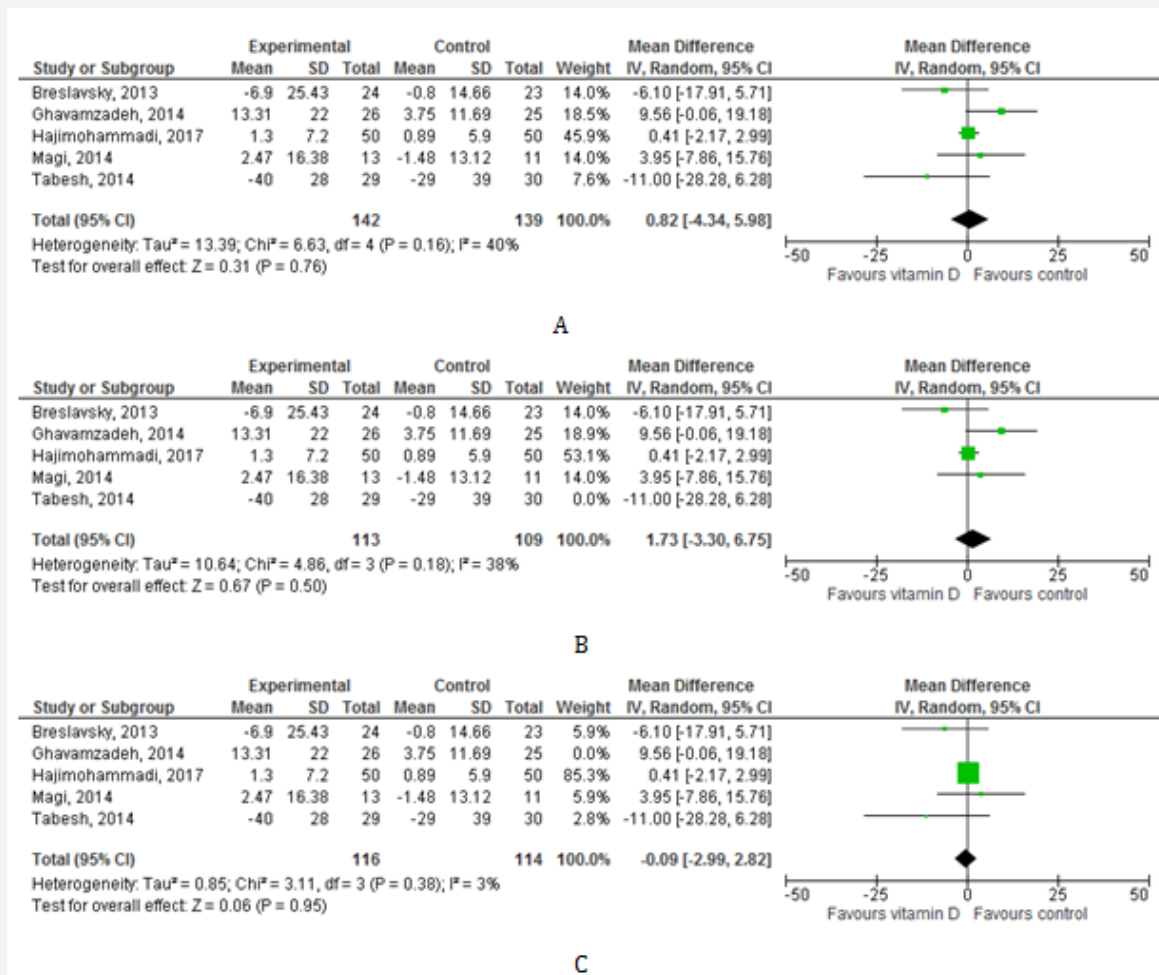


Figure 4: Effects of vitamin D supplementation on leptin levels (ng/ml). (A) Forest plot shows pooled mean differences with 95% confidence intervals (CI) for 5 randomized controlled trials. The green colored square represents the point estimate of the effect of the intervention for each trial. The horizontal line joins the upper and lower limits of the 95% CI of the effects. The square area represents the relative weight of the trial in the meta-analysis. (B) Eliminating Tabesh [99] and (C) Ghavamzadeh [92] in leave-one-out sensitivity analysis (the trials were given a relative weight of 0.0%).

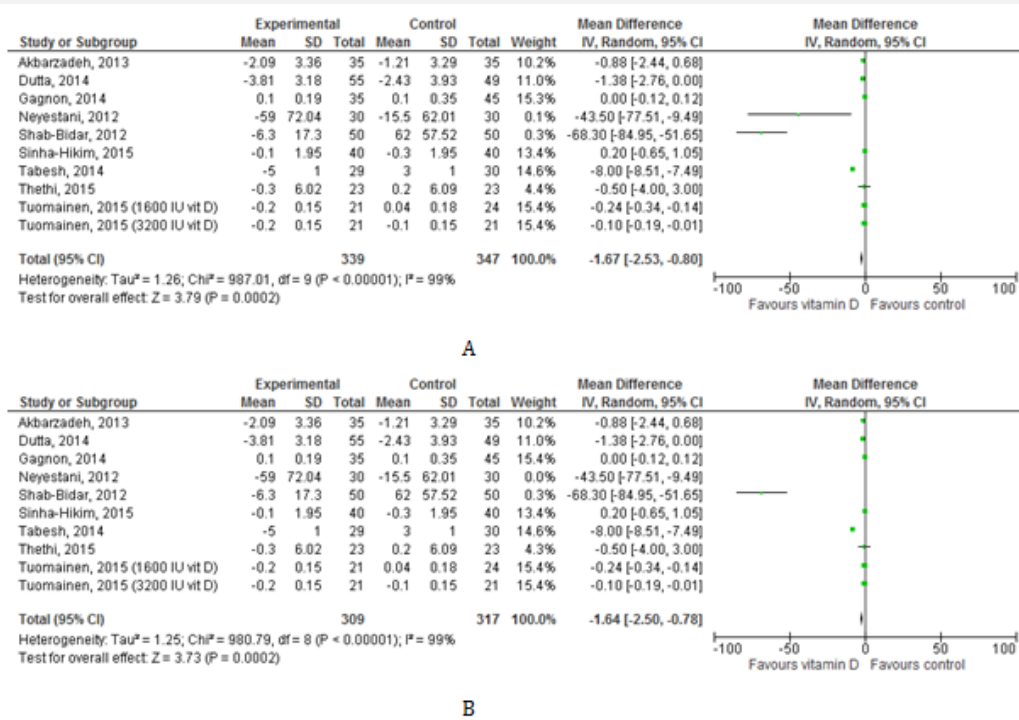


Figure 5: Effects of vitamin D supplementation on IL-6 levels (pg/ml). (A) Forest plot shows pooled mean differences with 95% confidence intervals (CI) for 10 intervention effects pooled from 9 randomized controlled trials (two separate effect sizes were pooled for two different dosing regimens of vitamin D in Tuomainen [101]). The green colored square represents the point estimate of the effect of the intervention for each intervention. The horizontal line joins the upper and lower limits of the 95% CI of the effects. The square area represents the relative weight of the interventions in the meta-analysis. (B) Eliminating Neyestani [96] and (C) Shab-Bidar [97] in leave-one-out sensitivity analysis (the trials were given a relative weight of 0.0%).

Table 1: Characteristics of randomized controlled trials included.

Reference	Sample Size, % Female	Age (Years, Mean ± SD)	BMI (kg/m ² , Mean ± SD)	Duration, design	Clinical condition/ Medication	Vit D Intervention	Comparison group	Outcome Parameters
Akbarzadeh [85]	70, 50%	Vit D: 53.8 ± 8.9, control: 52.4 ± 7.8	Vit D: 28.3 ± 4.4, control: 27.0 ± 3.4	12 weeks, parallel	Type 2 diabetes, Metformin, glybenclamide	0,5 µg Calcitriol (=1,25 dihydroxy-cholecalciferol) per day, orally	Placebo	IL-6
Al-Sofiani [86]	20; 25%	Vit D: 54.8 ± 9.16, control: 55 ± 11.99	Vit D: 28.8 ± 2.0, control: 33.5 ± 2.2	12 weeks, parallel	Type 2 diabetes, HbA1c ≥ 6, hypovitaminosis D, insulin resistance (HOMA-IR ≥ 2), hypoglycemic agents, lipid lowering drugs, antihypertensives	5.000 IU vit D ³ per day, orally	Placebo	Adiponectin, leptin, TNF-alpha, IL-6
Barchetta, 2016 [87]	55; Vit D: 30%, control: 40%	Vit D: 57.4 ± 10.7, control: 59.8 ± 9.1	Vit D: 29.3 ± 4.4, control: 30.8 ± 4.5	24 weeks, parallel	Type 2 diabetes, NAFLD, oral antidiabetics, insulin, statins, antihypertensives	2.000 IU vit D ₃ daily, orally	Placebo	Adiponectin
Baziar [88]	81; Vit D: 31.7, control: 35.0	Vit D: 50.34 ± 6.71, control: 52.75 ± 6.34	Vit D: 27.33 ± 1.64, control: 27.25 ± 1.35	8 weeks, parallel	Type 2 diabetes, hypovitaminosis D; Hypoglycemic agents, excluding insulin and thiazolidinediones	50.000 Vit D ³ per week, orally	Placebo	Adiponectin

Breslavsky [89]	47; Vit D: 54.2, control: 52.2	Vit D: 66.8 ± 9.2, control: 65.8 ± 9.7	Vit D: 27.9 ± 5.2, control: 30.6 ± 5.1	12 months, parallel	Type 2 diabetes, Oral antidiabetics: Metformin, Sulfonylurea, Repaglinide, DDP-4 inhibitors, insulin, Antihypertensives: ACEIs/ARBs, Diuretics, Beta blockers, CCBs	1.000 IU Vit D ³ per day, orally	Placebo	Leptin, adiponectin
Dutta [90]	104, Vit D: 63,2%, control: 54,3%	Vit D: 48.37 ±10.47, control: 47.4 ± 11.51	Vit D: 26.32 ± 4.52, control: 26.83 ± 4.63	At least one year follow up (Mean duration of follow up: Vit D: 28.2±8.83 months, control: 29.15±7.69 months), parallel	Prediabetes, hypovitaminosis D	60.000 vit D ³ per week, then once monthly, orally; along with 1250 mg calcium carbonate per day (500 mg elemental calcium)	1250 mg calcium carbonate per day (500 mg elemental calcium)	TNF-alpha, IL-6
Gagnon [91]	80; vit D: 71, control: 67	Vit D: 53.8 ± 11.9, control: 55.3 ± 11.1	Vit D: 31.1. ± 5.7, control: 31.9 ± 6.2	6 months, parallel	Multiethnic prediabetic individuals, hypovitaminosis D, no medications known to affect glucose and mineral metabolism over the last 3 months, no pharmacological treatment for obesity	Initially 2.000 IU vit D ³ and 1200 mg calcium per day, orally; dose of vitamin D increased by 2,000 IU every 2 months to reach a target of ≥75 nmol/L (final dose: 2.000-6.000 IU daily)	Placebo	Adiponectin, TNF-alpha, IL-6
Ghavamzadeh [92]	51; 58.8%	Vit D: 49.28 ± 2.00, control: 52.26 ± 2.09	Vit D: 28.9 ± 0.86, control: 27.9 ± 0.93	14 weeks, parallel	Type 2 diabetes, no other diseases, hypoglycemic agents, no insulin therapy	400 IU vit D ³ per day, orally	Placebo	Leptin, TNF-alpha
Hajimohammadi [93]	100, vit D: 62, C: 52	Vit D: 52.4 ± 8.4, C: 52.6 ± 6.3	Vit D: 28.6 ± 4.0, C: 30.0 ± 4.2	12 weeks, parallel	Type 2 diabetes	Fortified doogh: 1000 IU D3 + 340 mg calcium per day, orally	Plain doogh	Leptin
Magi [95]	30, Vit D: 35,7%, control: 12,5%	69	29	24 weeks, parallel	Type 2 diabetes, diabetic foot complications, 60 years and older	Single bolus dose of vit D ³ (300.000 IU), orally	Placebo	Leptin, adiponectin, TNF-alpha
Neyestani [96]	60, NR	Vit D: 51.5 ± 5.4, control: 50.8 ± 6.7	Vit D: 29.2 ± 4.4, control: 29.9 ± 4.7	12 weeks, parallel	Type 2 diabetes, not taking steroidal antiinflammatory or anticoagulant medications; no insulin therapy	Fortified doogh: 500 IU vit D3 daily, orally	Plain yoghurt drink or doogh	Adiponectin, IL-1 beta, IL-6, TNF-alpha, RBP-4
Shab-Bidar [97]	100; Vit D: 52%, control: 62%	30-60 years	NR	12 weeks, parallel	Type 2 diabetes, no insulin therapy, no weight reduction program, no history of other diseases	Fortified doogh: 500 IU vit D ³ twice daily (=1000 IU vit D3 per day), orally	Plain doogh	IL-6, TNF-alpha

Sinha-Hikim [98]	80; Vit D: 70, control: 70	Vit D: 51.6 ± 7.7, control: 52.4 ± 6.7	Vit D: 32.5 ± 4.4, control: 32.9 ± 4.5	12 months, parallel	Pre-diabetes, hypovitaminosis D, no medication	Average 85 300 IU ± 16 000 (range 64 700–134 000) Vit D ³ per week, orally	Placebo	TNF-alpha, IL-6
Tabesh [99]	59; vit D: 48, control: 53	Vit D: 50.2 ± 6.6, control: 51.0 ± 6.1	NR	8 weeks, parallel	Type 2 diabetes, hypovitaminosis D, hypoglycemic agents	50.000 IU Vit D ³ per week, orally	Placebo	Leptin, adiponectin, TNF-alpha, IL-6
Thethi [100]	55; Vit D: 35.7, control: 29.6	Vit D: 64 ± 9, control: 61 ± 10	NR	12 weeks, parallel	Type 2 diabetes, Chronic kidney disease stage 3 or 4, hypoglycemic agents, ACEIs/ ARBs, Statins	Paracalcitol 1 mcg daily, orally	Placebo	TNF-alpha, IL-6
Tuomainen [101]	66; NR	65.7 ± 7.0	29.4 ± 2.7	5 months, parallel	Prediabetic individuals, at least 60 years of age, overweight but not severely obese (BMI between 25 and 35), serum 25(OH) D ³ concentration <75 nmol/L	Two groups: 40 µg (equivalent to 1600 IU) or 80 µg (3200 IU) vit D ³ per day, orally	Placebo	Adiponectin, IL-6

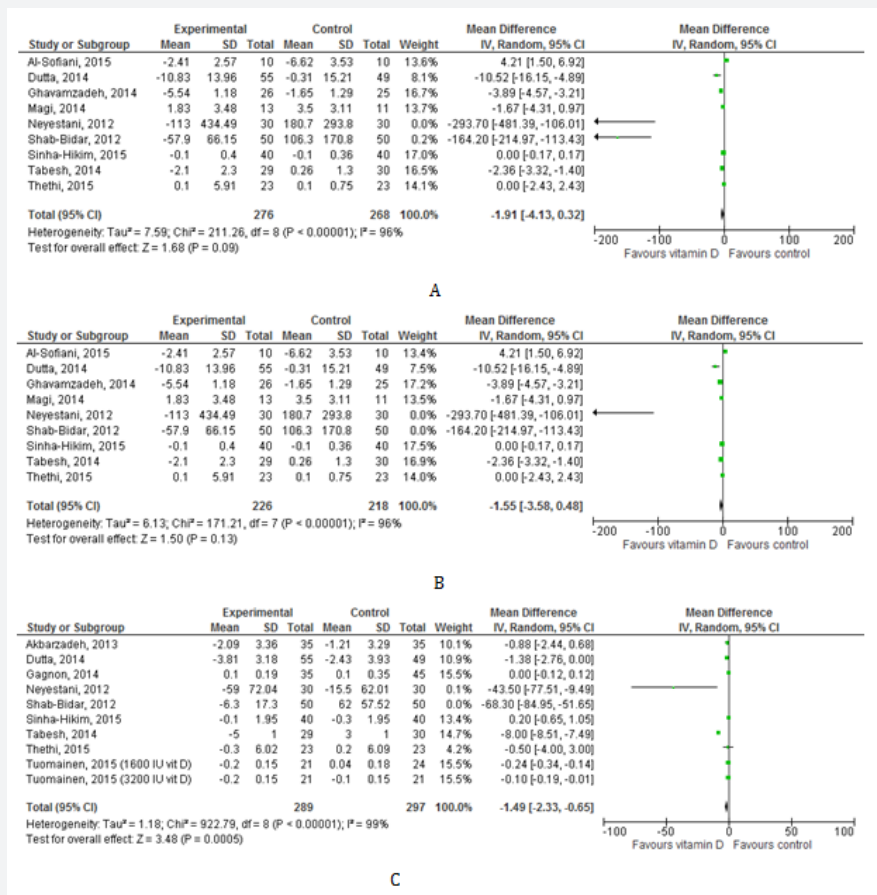


Figure 6: Effects of vitamin D supplementation on TNF-alpha levels (pg/ml). (A) Forest plot shows pooled mean differences with 95% confidence intervals (CI) for 9 randomized controlled. The green colored square represents the point estimate of the effect of the intervention for each intervention. The horizontal line joins the upper and lower limits of the 95% CI of the effects. The square area represents the relative weight of the interventions in the meta-analysis. (B) Eliminating Shab-Bidar [97] as part of the leave-one-out sensitivity analysis (the trial was given a relative weight of 0.0%).

Vitamin D supplementation significantly reduced levels of IL-6, but with considerable study heterogeneity (MD: -1.67 pg/ml (95% CI -2.53, -0.80), $p = 0.0002$, $I^2 = 99\%$) (Figure 5a). Removing Neyestani 96 (MD: -1.64 pg/ml (95% CI -2.50, -0.78), $p = 0.0002$, $I^2 = 99\%$) (Figure 5b) and Shab-Bidar 97 (MD: -1.49 pg/ml (95% CI -2.33, -0.65), $p = 0.0005$, $I^2 = 99\%$) (Figure 5c) from the analysis did not significantly change the effect size, which can be explained by the very low relative weights these studies had in the original meta-analysis. TNF-alpha levels were also reduced by vitamin D supplementation, but the effects were not statistically significant and study heterogeneity was

high (MD: -1.91 pg/ml (95% CI -4.13, 0.32), $p = 0.09$, $I^2 = 96\%$) (Figure 6a). No significant changes in effect size were seen once we removed Shab-Bidar 97 for the sensitivity analysis (MD: -1.55 pg/ml (95% CI -3.58, 0.48), $p = 0.13$, $I^2 = 96\%$) (Figure 6b) (Table 1).

Inspection Of Publication Bias

The visual inspection of funnel plots (Figure 7) showed an asymmetry for the inspected outcomes, except for leptin. This implies that for most of the outcomes inspected in present work, a publication bias cannot be excluded with certainty.

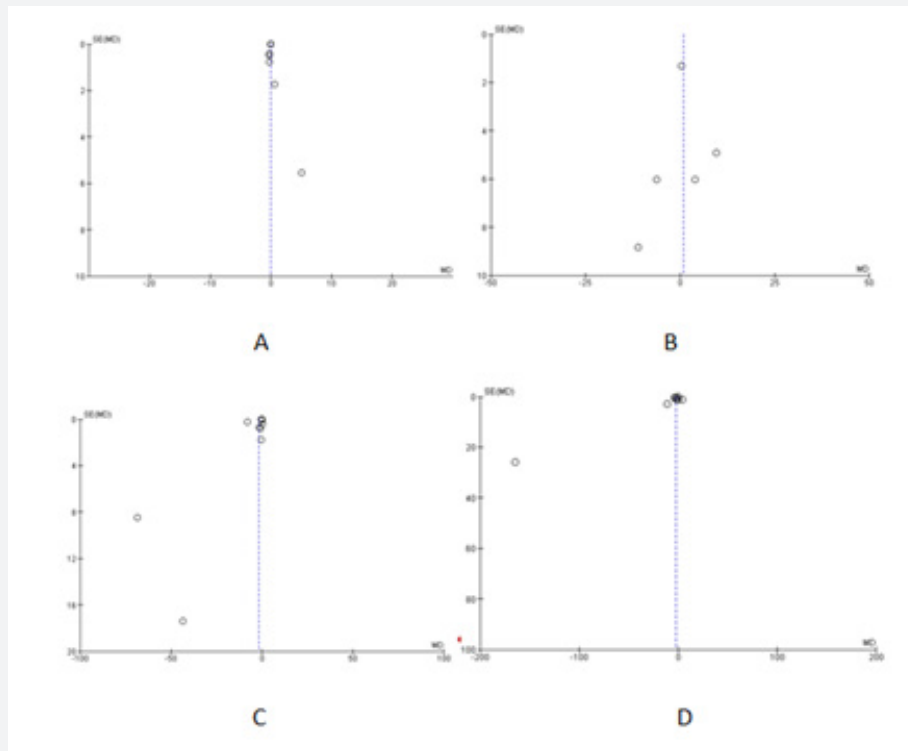


Figure 7: Funnel plot showing study precision against the mean difference effect estimate with 95% confidence interval for (A) adiponectin, (B) leptin, (C) IL-6 and (D) TNF-alpha. SE = standard error.

Discussion

The prevalence of inadequate vitamin D levels in populations across the globe go hand-in-hand with the ever-growing diabetes burden. However, the extent to which reaching and maintaining adequate vitamin D levels affect glucose metabolism and prevent the development of its pathological dysregulation is not entirely known. While it is plausible that being deficient bares a higher risk for diabetes [102], supplementation has yielded mixed results in studies in diseases individuals [52-66]. Given this inconsistency and the emerging wealth of evidence regarding the importance of adipocytokines in prediabetes and diabetes, we set out to investigate the effects of vitamin D supplementation in this group.

In the present systematic review and meta-analysis, we demonstrate that vitamin D can indeed affect circulating levels

of some adipocytokines. In general, we observed no effects on adiponectin, while leptin levels as outcome was sensitive to individual studies and overall inconclusive, but after reducing study inconsistency to the lowest level, the size of the effect was negligible. These results are in line with another recent meta-analysis, which also found no significant effects of vitamin D supplementation on levels of adiponectin and leptin, though this meta-analysis was not restricted solely to prediabetic and diabetic individuals [103].

On the other hand, IL-6 and TNF-alpha levels were reduced by vitamin D supplementation, although the results were statistically significant only for IL-6. This is in contrast with a previous meta-analysis involving overweight and obese individuals which found no effects of supplementing vitamin D on these inflammatory biomarkers [104]. A study employing high-sensitivity assay

found the upper 95th percentile reference limit for IL-6 to be 4.45pg/ml, and for TNF-alpha 2.53pg/ml [105]. However, in prediabetic individuals a 4-fold and 10-fold increase in levels of IL-6 and TNF-alpha was described, respectively [106], and 10-fold and 50-fold in obese diabetic individuals [107]. Therefore, the effect size we found, i.e. less than 2 pg/ml reduction for both cytokines, is unlikely to be of clinical relevance that would bring about significant amelioration of complications associated with increased levels of these pro-inflammatory cytokines.

Our study has several limitations. Overall, we observed high study heterogeneity. Most studies did not provide sufficient information in order to be able to judge on the risk of bias across all of the predetermined criteria. Also, the studies included did not take into account seasonal variations in vitamin D status. Sun exposure is suggested to be associated with serum 25-hydroxy vitamin D levels more strongly than vitamin D supplementation [108]. The studies included populations with mixed characteristics in terms of sex distribution, age, body weight, vitamin D status, co-pathologies and medication use. Also, vitamin D supplementation interventions were heterogeneous among the studies, including chemical form, supplement type, intervention duration and dose. Calcium supplementation also formed part of the intervention in some studies; calcium is suggested to exert effects on body weight [109], which in turn could also have an influence on adipocytokine levels. In addition, we could not exclude publication bias in most of the outcomes analysed. Given these limitations, the results of the current meta-analysis should be interpreted with caution.

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