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Vitamin D Supplementation Does not Affect Serum Leptin and Adiponectin Levels in Adults: A Systematic Review and Meta-analysis of Randomised Controlled trials

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ABSTRACT

Background & aims: It is proposed that vitamin D supplementation might influence serum adipokines level; however, the recent meta-analyses have led to inconsistent results while they had methodological limitations. Therefore, this study aimed to examine the effects of vitamin D supplementation on serum adipokines through a systematic review and a meta-analysis of randomized placebo-controlled trials (RCTs) using a more comprehensive search strategy.

Methods: PubMed, Google Scholar, and Scopus were searched to identify related articles published up to November 2017. Mean±standard deviation (SD) of changes in serum adiponectin and leptin were extracted, and the effect sizes were pooled using a random-effects model.

Studies with Controlled clinical trials design were eligible. Two reviewers extracted mean values and SDs of the baseline, final and net change values of leptin and adiponectin in the intervention and control groups.

Results: The pooled results indicated that vitamin D supplementation affects neither circulating leptin (Hedges' g = 0.042, 95% CI: -0.294 to 0.378, p = 0. 0.807, n=15) nor adiponectin (Hedges' g = -0.034, 95% CI: -0.243 to 0.174, p = 0.748, n=18) levels. Subgroup analysis showed that vitamin D supplementation might significantly decrease serum leptin level in patients with end stage renal disease (Hedges' g = -0.634, 95 % CI: -1.221 to -0.047, p = 0.034).

Conclusions: Although the current evidence does not support the significant effect of vitamin D supplementation on adiponectin and leptin levels, further research is required to reach more definitive conclusions.

Keywords: Vitamin D, Leptin, Adiponectin, Systematic review, Meta-analysis

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Introduction

Obesity is considered as a significant nutritional problem in low, middle and high-income countries *[1]*. The urbanization and considerable changes in lifestyle are associated with the high prevalence of overweight and obesity, especially in developing countries *[2]*. It is estimated that more than 57.8% of the world's adult population will suffer from overweight or obesity by 2030 *[2]*. Obesity is linked to the increased rate of morbidity and mortality, which may create massive socio-economic and public

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health burdens for poorer nations *[1]*. Moreover, overweight and obesity increase the risk of diabetes, cardiovascular disease, cancer and premature death *[3]*.

Obesity is defined as an accumulation of large amounts of fat mass in the body *[4, 5]*. The fat mass secretes bioactive peptides, named adipokines, which have an essential role in several processes, including food intake, insulin action, lipid, and glucose metabolism and regulation of the energy balance *[6, 7]*. The dysfunction in adipokines' pathways is considered as an important reason for diseases caused by obesity *[6, 7]*. Leptin and adiponectin are well-known adipokines that are involved in the regulation of metabolic homeostasis, especially obesity *[8]*. It is suggested that serum levels of adiponectin and leptin are negatively and positively associated with body fat, respectively *[8]*. Studies have shown that the reduction in circulating adiponectin concentrations in obese subjects might increase the risk of obesity, insulin resistance, diabetes, metabolic syndrome, cardiovascular disease and hypertension *[9, 10]*. Leptin is another adipokine that inhibits appetite and increases energy expenditure by influencing specific receptors in the hypothalamus when body fat is elevated *[11]*.

Recently, the association between vitamin D deficiency and obesity and its possible mechanisms has been considered by investigators *[12]*. A meta-analysis of observational studies indicated a significant inverse association between serum 25 (OH) D levels and BMI *[13]*. However, the meta-analysis of clinical trials did not show the significant effect of vitamin D supplementation on body weight *[14, 15]*, fat mass *[14, 15]*, percentage of fat mass or lean body mass *[15]*, and body mass index (BMI) *[14, 16]*. Besides, it is proposed that vitamin D might affect adipokines. Observational studies suggest that serum 25 (OH) D levels are positively correlated with adiponectin, and inversely correlated with leptin *[17, 18]*.

In contrast, a number of clinical trials showed that vitamin D supplementation might increase the plasma levels of leptin *[19, 20]* and decrease serum adiponectin levels *[21]*. On the other hand, some other studies reported the reduction in serum leptin levels *[22]* and the increase in serum adiponectin levels *[23, 24]* after vitamin D supplementation. However, some clinical trials did not show any significant effect *[25-27]*. Recently, two meta-analyses of clinical trials *[28, 29]* tried to summarize the effect of vitamin D supplementation on leptin and adiponectin levels, but their results were inconsistent. While no significant effect of vitamin D supplementation on leptin and adiponectin was reported in a study by Dinca et al. *[28]*, the other study concluded that serum level of leptin is significantly increased following vitamin D supplementation *[29]*. While both meta-analyses have adopted the same search strategies, different studies were included in their analysis, and consequently, the different findings were found. Furthermore, it is claimed that the number of included studies in both meta-analyses were limited and more clinical trials are needed in this regard. The present study attempted to elucidate the effect of vitamin D supplementation on plasma leptin and adiponectin concentrations by conducting an updated systematic review and meta-analysis.

Materials And Methods

The present systematic review is reported based on the preferred reporting items for systematic reviews and meta-analysis (PRISMA) guidelines. The study protocol was also registered in the prospective international register of systematic reviews (PROSPERO) under the registry number of CRD 42018092110.

Search strategy

This systematic review and meta-analysis evaluated the effect of vitamin D supplementation on serum adiponectin and leptin levels through reviewing controlled clinical trials conducted in

humans. The electronic databases including PubMed, Google Scholar, and Scopus were searched until November 2017, using two sets of the following MeSH and non-MeSH keywords: 1) "Vitamin D" OR "Ergocalciferols" OR "Cholecalciferol" OR "Calcitriol" OR "Calcifediol" OR "25-Hydroxyvitamin D 2" OR "25-hydroxyvitamin D" OR "1-25-dihydroxy-23,23-difluorovitamin D3" OR "25(OH)D" OR "25-OH vitamin D" OR "1,25 (OH) (2) D" OR "1,25 (OH) D" OR "1,25-(OH) (2) D (3)" OR "25-hydroxyvitamin D" OR "Vitamin D" OR "25-(OH) D (3)" OR "25-(OH) D (2)" OR "Ergocalciferols" OR "Cholecalciferol" OR "Calcitriol" and 2) "Intervention Studies" OR "intervention" OR "controlled trial" OR "randomized" OR "randomised" OR "random" OR "randomly" OR "placebo" OR "assignment" OR "clinical trial" OR "trial" And "Adipocytokines" OR "Adipokine" OR "Adiponectin" OR "Adipokines" OR "leptin." The wild-card term "*" was used to increase the sensitivity of the search strategy. The search was conducted in the title, abstract and keywords without language limitation. Furthermore, the reference lists of retrieved articles were also reviewed for additional studies. All these steps were performed by two researchers individually (SJS and SS), and disagreements were resolved by discussion.

Study selection

The original studies were included if they met the following criteria: 1) being conducted in human adults, 2) being controlled clinical trial in design (either parallel or cross-over), 3) vitamin D supplementation was considered as an intervention, 5) measured and reported leptin and adiponectin concentrations were reported as an outcome at baseline and the end of follow-up in each group or provided the net change values.

Data extraction

Eligible studies were reviewed, and the following information was extracted: lead author's last name, year of publication, study location, study design, participant's gender, the sample size of vitamin D and control groups, type and dose of vitamin D, participants' characteristic, duration of the treatment, mean values and SD of the baseline. Ultimately, final concentrations and net changes of leptin and adiponectin were extracted independently by two reviewers (SJ, SS) in the intervention and control groups.

Quality assessment

Quality of the included articles was evaluated using the Cochrane Collaboration's tool *[30]* based on the following domains: sequence generation (selection bias), allocation sequence concealment (selection bias), blinding of participants and outcome assessors (performance and detection bias, respectively), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias) and other potential sources of bias. The risk of bias was measured as 'low risk,' 'high risk or "unclear risk." The included studies were classified as fair if they were at low risk for two domains and good if they were low risk in more than two domains.

Statistical analysis

The difference in mean change (MD) for serum leptin, adiponectin levels and their corresponding standard deviation (SD) were calculated for each study. In case of not reporting the mean and SD for mean change values, they were estimated using correlation coefficient for studies which reported the baseline, after follow-up and change values (r = 0.57 for leptin *[20, 31-33]* and r = 0.59 for adiponectin *[20, 23, 24, 31, 34, 35]*. To check the sensitivity of the meta-analyses to calculated correlation coefficients, the meta-analyses were replicated by computing the effect sizes based on r = 0.2 and r = 0.8. The Hedges' g and its corresponding standard error (SE) were calculated as the effect size to perform the meta-analysis because the values were reported in different scales, and the conversion was not possible. The meta-analyses were done using a

random-effects model, which takes the between-study heterogeneity into account. Statistical heterogeneity between studies was examined using the Cochran's Q test and I-squared *[36]*. Subgroup analysis was conducted to evaluate the sources of between studies heterogeneity. In order to explore the extent to which inferences might depend on a particular study or group of studies, a sensitivity analysis was performed by recalculating the pooled effects after 1) removing the highest-weighted study from a given analysis (the "leave-one-out" analysis) *[37]*; and 2) testing alternatives by the 0.5 correlation between baseline and post-treatment values (0.2 and 0.8). Publication bias was examined by visual inspection of funnel plots *[38]*. In this funnel, effect sizes were depicted against their corresponding SE. Statistical assessment of funnel plot asymmetry was tested using two formal tests, the Begg's adjusted rank correlation tests and the Egger's regression asymmetry test *[39]*. Statistical analyses were conducted using STATA version 11.0 (STATA Corp. College Station, Texas). P-values less than 0.05 was considered to be a significant difference.

Results

After the initial search, 4,929 articles were identified, and 227 duplicates were removed. The screening of the title/abstracts led to 416 articles which their full-text were assessed for eligibility; 393 items were eliminated because they did not have the inclusion criteria and did not measure adipokines as the outcome variable. Finally, 23 studies were entered into the systematic review and 22 studies in the meta-analysis (**Figure 1**). The plasma adiponectin concentrations were evaluated in 19 RCTs *[20-27, 31, 33-35, 40-46]* and 16 RCTs *[19, 20, 22, 25-27, 31-33, 40-42, 44, 46-48]* reported data on plasma leptin concentrations. The included studies have been published between 2009 to 2017. Among the twenty-three studies, twelve were conducted in Asia *[19, 22-24, 31-35, 40, 43, 48]*, three in America *[25, 41, 47]*, six in Europe *[20, 26, 27, 42, 44, 45]* and two in Australia *[21, 46]*. In the included studies, 858 participants were assigned to vitamin D supplementation, and 846 were assigned as controls. Two studies *[27, 41]* were conducted in only females, and others were done in both sexes. The study duration ranged from 1 to 48 weeks.

Twelve studies administered daily doses *[19, 21, 24-26, 31, 32, 40, 41, 44, 45, 47]*, four studies managed weekly doses *[22, 33, 34, 43]*, two studies did monthly doses *[46, 48]*, one study prescribed vitamin D for every two weeks *[35]*, and four studies used a single bolus dose *[20, 23, 27, 42]*. Fourteen studies were conducted on participants with vitamin D deficiency *[21-23, 25, 27, 31, 33, 34, 40-42, 45, 47, 48]*. The doses of vitamin D supplementation varied from 400 IU to 10000 IU/day in multiple daily doses prescription and 300000 IU to 600000 IU when single bolus doses were prescribed. All randomized clinical trials have a parallel design. So, if a study used different doses of vitamin D *[46]*, it is included the highest dose in the meta-analysis. Besides, one study investigated different types of vitamin D, including ergocalciferol and cholecalciferol for intervention *[44]*. Therefore, the data for vitamin D_3 supplementation was included.

Furthermore, the data of both male and female sex was combined in a study conducted by Sharifi et al. *[35]*, and then they were analyzed. The researchers of this study contacted the corresponding author of Al-Sofiani et al. study *[40]* for data regarding the serum level of leptin and adiponectin. However, a requested data were not provided. So, the study was included in the systematic review but not in the meta-analysis. The characteristics of the included studies are shown in **Table 1**. One study did not report the final measurement of adipokines *[40]*; thus this study was also excluded from the meta-analysis.

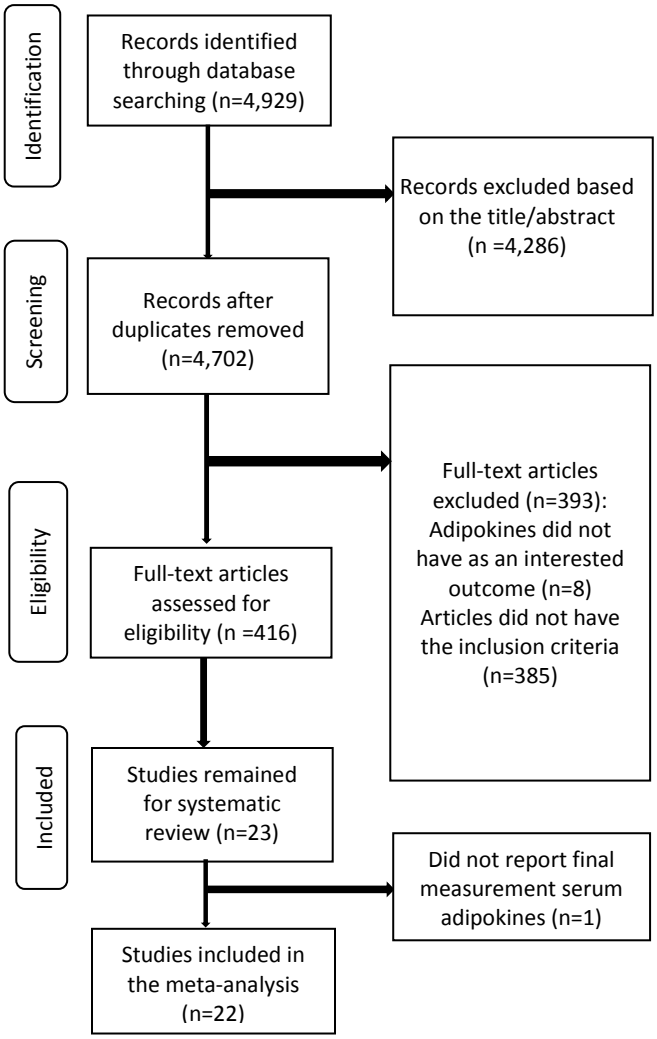


Figure 1: Study selection process

Risk of bias in individual studies

The result of evaluating the bias assessment in included studies is presented in **Table 2**. A high risk of bias was assessed according to random sequence generation *[48]*, allocation concealment *[48]*, blinding of participants and outcome assessors *[32, 42, 48]*, and incomplete outcome data *[44]* in a number of studies. Some trials were classified as unclear risk of bias regarding allocation concealment *[20-25, 31, 33, 41, 42, 44-46]*, blinding of participants and outcome assessors *[45]*; but all studies *[19-27, 31-35, 41-48]* were low-risk in terms of other sources of bias. The overall quality of all the included studies was assessed to be good.

The effect of vitamin D supplementation on serum leptin levels

As shown in **Figure 2**, the meta-analysis of 15 studies *[19, 20, 22, 25-27, 31-33, 41, 42, 44, 46-48]* did not show any significant effect of vitamin D supplementation on serum leptin levels (Hedges' g = 0.042, 95 % CI: -0.294 to 0.378, p = 0.807). There was a high-level of heterogeneity between included studies (Cochrane Q test, Q statistic = 93.79, P < 0.001, I^2 = 85.1%). Subgroup analyses were performed based on baseline vitamin D status, disease status (with/without diabetes), kidney disease status (yes/no) of participants, vitamin D type used for supplementation, vitamin D supplementation method (single dose/daily/weekly/two weeks/ monthly), participants' sex, study duration, and vitamin D fortification (yes/no) to evaluate whether the effect is different in a specific group of studies or not. Vitamin D supplementation significantly decreased serum leptin level in patients with end-stage renal disease (ESRD) (Hedges' g = -0.634, 95 % CI: -1.221 to -0.047, P = 0.034). However, the serum leptin increased significantly when a single dose of vitamin D supplementation was prescribed (Hedges'g = 0.941, 95 % CI: 0.368 to 1.514, p = 0.001). Besides, subgroup analysis revealed that study duration was another source of heterogeneity. The results of this study were not sensitive to the selected correlation coefficient (**Table 3**)

Table 1. Characteristics of randomized controlled trials that evaluated the effect of vitamin D supplementation on serum leptin and adiponectin that were eligible to be included in the systematic review

First author Publication year	Country	Gender (No. of participants)	Duration (week)	Subjects characteristic	Supplementation strategy		Results
					Intervention	control	
Tarcin, 2009*[48]*	Turkey	Both (27)	12	Young, healthy volunteers with 25(OH)D deficiency	300000 IU/month vitamin D3 as an intramuscular injection	placebo	Leptin was significantly increased
O'Sullivan, 2011*[26]*	Ireland	Both (160)	4	Healthy subjects	600 IU/day vitamin D3	placebo	No significant effect on leptin and adiponectin
Chai, 2012*[47]*	USA	Both (92)	24	Healthy volunteers	800 IU/daily given twice a day as an oral dose (400 IU) vitamin D3	placebo	No significant effect on leptin
Neyestani, 2012*[24]*	Iran	Both (60)	12	Type 2 diabetic patients	500 IU/day vitamin D3 plus 150 mg calcium as the dough	150 mg calcium as the dough	Adiponectin was significantly increased
Breslavsky, 2013*[31]*	Israel	Both (47)	48	Type 2 diabetic patients	1000 IU/day vitamin D3	placebo	No significant effect on leptin but adiponectin marginally increased
Hung, 2013*[25]*	USA	Both (10)	8	Chronic hemodialysis patients	Paricalcitol	cinacalcet	No significant effect on leptin and adiponectin
Petchey,2013 *[21]*	Australia	Both (51)	24	Patients with stage 3 Chronic Kidney Disease	2000 IU/day vitamin D3	placebo	Adiponectin was significantly decreased
Stepien, 2013*[44]*	Ireland	Both (43)	4	Healthy subjects	600 IU/day vitamin D3	placebo	No significant effect on leptin and adiponectin
Wamberg, 2013 *[45]*	Denmark	Both (55)	26	Obese subjects with low plasma levels of 25 (OH) D	7000 IU/day vitamin D3	placebo	No significant effect on adiponectin
Witham, 2013*[27]*	UK	Female (50)	8	Healthy women	A single dose of 100,000 IU vitamin D3	placebo	No significant effect on leptin and adiponectin
Baziar, 2014*[34]*	Iran	Both (87)	8	Type 2 diabetic patients with 25 (OH) D insufficiency or deficiency	50000 IU/week vitamin D	placebo	No significant effect on adiponectin
Ghavamzadeh, 2014*[19]*	Iran	Both (51)	14	Type 2 diabetic patients	400 IU/day vitamin D3	placebo	Leptin was significantly increased
Maggi, 2014*[20]*	Italy	Both (30)	24	Type 2 diabetes and diabetic foot complications	A single dose of 300,000 IU vitamin D3	placebo	Leptin increased but No significant effect on adiponectin

First author Publication year	Country	Gender (No. of participants)	Duration (week)	Subjects characteristic	Supplementation strategy		Results
					Intervention	control	
Tabesh, 2014*[22]*	Iran	Both (120)	8	Type 2 diabetic patients with 25 (OH) D insufficiency	50000 IU/week vitamin D3	Placebo	Leptin was significantly decreased but no significant effect on adiponectin
Al-Sofiani, 2015*[40]*	Saudi Arabia	Both (22)	12	Type 2 diabetic with hypovitaminosis D	5000 IU/day vitamin D3	Placebo	No significant effect on leptin and adiponectin
Duggan, 2015*[41]*	USA	female (218)	48	Obese subjects with 25 (OH) D deficiency	2000 IU/day vitamin D3 plus weight-loss intervention	Placebo plus weight-loss	No significant effect on leptin and adiponectin
Waterhouse, 2015*[46]*	Australia	Both (644)	48	Healthy adult	60000 IU/month vitamin D3	placebo	No significant effect on leptin and adiponectin
Alizadeh, 2016*[23]*	Iran	Both (59)	1	Adult surgical patients with hyperglycemia	A single dose of 600,000 IU vitamin D3 as an intramuscular injection	placebo	Adiponectin was significantly increased
Mohammadi, 2016 *[43]*	Iran	Both (64)	12	Type 2 diabetic patients	50000 IU/week vitamin D3 plus lifestyle change	Placebo plus lifestyle change	No significant effect on adiponectin
Naini, 2016*[33]*	Iran	Both (64)	12	ESRD patients undergoing hemodialysis with vitamin D deficiency	50000 IU/week vitamin D3	Placebo	Leptin decreased and adiponectin increased
Sharifi, 2016*[35]*	Iran	Both (53)	16	Patients with non-alcoholic fatty liver disease (NAFLD)	50000 IU/2weeks vitamin D3	Placebo	No significant effect on adiponectin
Hajimohammadi, 2017 *[32]*	Iran	Both (100)	12	Type 2 diabetic patients	500 IU vitamin D3 and 170 mg calcium as dough twice a day	170 mg calcium as dough twice a day	Leptin was significantly increased
Mai, 2017*[42]*	Italy	Both (26)	4	Obese subjects with vitamin D deficiency	A single dose of 600,000 IU vitamin D3 plus caloric restriction and aerobic physical exercise	caloric restriction and aerobic physical exercise	No significant effect on leptin and adiponectin

Table 2. Study quality and risk of bias assessment using the Cochrane collaboration tool

Study	Sequence generation	Allocation concealment	Blinding of participants, personnel and outcome assessors	Incomplete outcome data	Selective outcome reporting	Other potential threats to validity	Total scores	Overall quality
Tarcin (2009)*[48]*	H	H	H	L	L	L	3	good
O'Sullivan (2011)*[26]*	L	L	L	L	L	L	6	good
Chai (2012) *[47]*	L	L	L	L	L	L	6	good
Neyestani (2012) *[24]*	L	U	L	L	L	L	5	good
Breslavsky (2013)?*[31]*	L	U	L	L	L	L	5	good
Hung (2013)*[25]*	L	U	L	L	L	L	5	good
Petchey (2013)*[21]*	L	U	L	L	L	L	5	good
Wamberg (2013)*[45]*	L	U	U	L	L	L	4	good
Witham (2013)*[27]*	L	L	L	L	L	L	6	good
Baziar (2014)?*[34]*	L	L	L	L	L	L	6	good
Ghavamzadeh (2014)?*[19]*	L	L	L	L	L	L	6	good
Maggi (2014) *[20]*	L	U	L	L	L	L	5	good
Stepien (2014)*[44]*	L	U	L	H	L	L	4	good
Tabesh (2014)*[22]*	L	U	L	L	L	L	5	good
Al-Sofiani (2015)*[40]*	L	L	L	L	H	L	5	good
Duggan (2015)*[41]*	L	U	L	L	L	L	5	good
Waterhouse (2015)*[46]*	L	U	L	L	L	L	5	good
Alizadeh (2016)*[23]*	L	U	L	L	L	L	5	good
Mohammadi (2016)*[43]*	L	L	L	L	L	L	6	good
Naini (2016)*[33]*	L	U	L	L	L	L	5	good
Sharifi (2016)*[35]*	L	L	L	L	L	L	6	good
Hajimohammadi (2017)*[32]*	L	L	H	L	L	L	5	good
Mai (2017)*[42]*	L	U	H	L	L	L	4	good

L: Low; H:High

Table 3. Meta-analysis showing the effect of vitamin D supplementation on serum leptin based on several subgroups (all analyses were conducted using a random-effects model).

Study group	Number of studies	Meta-Analysis		Heterogeneity			P for between group
		Hedges'g (95%CI)	P for effect	Q statistic	P for within group	I^2 (%)	
Overall	18	-0.034 (-0.243, 0.174)	0.748	51.44	<0.001	67.0	--
Baseline vitamin D status							
Normal	7	-0.031 (-0.172, 0.110)	0.666	5.58	0.472	--	0.970
Deficiency	11	-0.108 (-0.487, 0.271)	0.577	45.86	<0.001	78.2	
Type 2 diabetes mellitus							
Without diabetes	12	-0.004 (-0.179, 0.172)	0.966	17.07	0.106	35.6	0.702
With diabetes	6	-0.091 (-0.697, 0.515)	0.768	34.22	<0.001	85.4	
Kidney disease							
Without ESRD[1]	15	-0.027 (-0.245, 0.191)	0.811	43.99	<0.001	68.2	0.851
With ESRD	3	-0.151 (-1.057 , 0.755)	0.744	7.42	0.025	73.0	
Vitamin D type							
Vitamin D3	17	-0.026 (-0.240, 0.187)	0.808	51.15	<0.001	68.7	0.589
Vitamin D2	1	-0.343 (-1.472, 0.787)	0.552	0.00	--	--	
Vitamin D administration							
Single dose	4	0.229 (-0.269, 0.727)	0.367	5.42	0.144	44.6	
Daily	8	-0.007 (-0.207, 0.194)	0.947	8.78	0.269	20.2	
Weekly	4	-0.219 (-1.090, 0.652)	0.622	32.48	<0.001	90.8	0.312
2 Weeks	1	-0.118 (-0.649, 0.413)	0.663	0.00	--	--	
Monthly	1	-0.084 (-0.277, 0.109)	0.394	0.00	--	--	
Gender							
Both	14	-0.022 (-0.279, 0.235)	0.866	50.42	<0.001	72.2	
Female	3	0.002 (-0.238, 0.242)	0.987	0.85	0.655	--	0.776
male	1	-0.281 (-1.029, 0.468)	0.462	0.00	--	--	
Study duration							
Short term (<8weeks)	8	-0.217 (-0.693, 0.259)	0.372	36.34	<0.001	80.7	0.088
Long term (≥8 weeks)	10	0.063 (-0.106, 0.232)	0.468	12.20	0.202	26.2	
Fortification							
No fortification	17	-0.066 (-0.279, 0.147)	0.544	47.73	<0.001	66.5	0.054
Fortified foods	1	0.454 (-0.052, 0.960)	0.079	0.00	--	--	

[1] ESRD: End-stage renal disease

Table 4. Meta-analysis indicated the effect of vitamin D supplementation on serum adiponectin based on several subgroups (all analyses were conducted using a random-effects model).

Study group	Number of studies	Meta-Analysis		Heterogeneity			P for between group
		Hedges'g(95%CI)	P for effect	Q statistic	P for within group	I^2 (%)	
Overall	15	0.042 (-0.294,0.378)	0.807	93.79	<0.001	85.1	--
Baseline vitamin D status							
Normal	7	0.108 (-0.089, 0.305)	0.283	8.45	0.207	29.0	0.205
Deficiency	8	-0.100 (-0.867, 0.667)	0.798	83.73	<0.001	91.6	
Type 2 diabetes mellitus							
Non diabetic	10	0.133 (-0.163, 0.429)	0.379	31.98	<0.001	71.9	0.353
Diabetic	5	-0.176 (-1.212, 0.860)	0.739	60.94	<0.001	93.4	
Kidney disease							
Without ESRD	13	0.118 (-0.239, 0.476)	0.517	86.54	<0.001	86.1	0.013
With ESRD	2	-0.634 (-1.221, -0.047)	0.034	1.12	0.290	10.7	
Vitamin D type							
Vitamin D3	14	0.050 (-0.298, 0.398)	0.778	93.74	<0.001	86.1	0.828
Vitamin D2	1	-0.122 (-1.242, 0.999)	0.832	<0.001	--	--	
Vitamin D administration							
Single dose	3	0.941 (0.368, 1.514)	0.001	0.19	0.910	--	<0.001
Daily	8	0.056 (-0.100, 0.212)	0.479	3.92	0.789	--	
Weekly	2	-1.651 (-3.315, 0.013)	0.052	13.45	<0.001	92.6	
Monthly	2	0.664 (-0.761, 2.090)	0.361	18.30	<0.001	94.5	
Gender							
Both	13	0.049 (-0.345, 0.444)	0.806	93.71	<0.001	87.2	0.795
Female	2	-0.029 (-0.293, 0.234)	0.827	0.01	0.903	--	
Study duration							
Short term (<8weeks)	6	-0.289 (-1.297, 0.719)	0.575	54.91	<0.001	90.9	0.030
Long term (≥8 weeks)	9	0.199 (-0.105, 0.503)	0.199	34.14	<0.001	76.6	
Fortification							
No fortification	14	0.041 (-0.328, 0.411)	0.826	93.69	<0.001	86.1	0.754
Fortified foods	1	0.062 (-0.327, 0.451)	0.756	0.00	--	--	

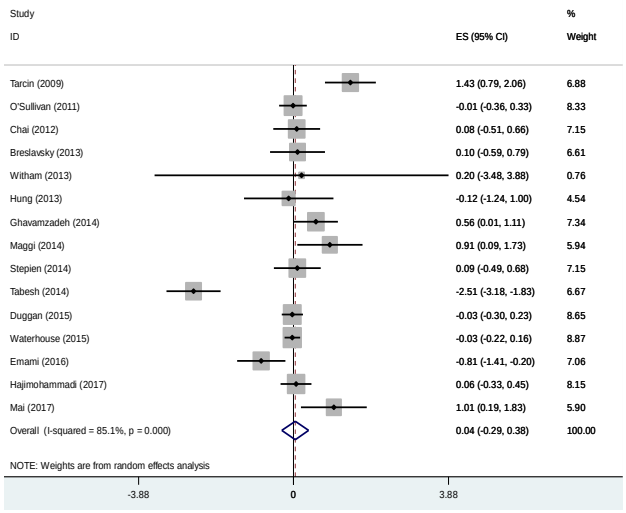


Figure 2. Forest plot of randomized controlled clinical trials illustrating standardized mean difference (Hedges' g) in serum leptin concentration change between the vitamin D supplementation and control groups for all eligible studies. The analysis was conducted using the random-effects model.

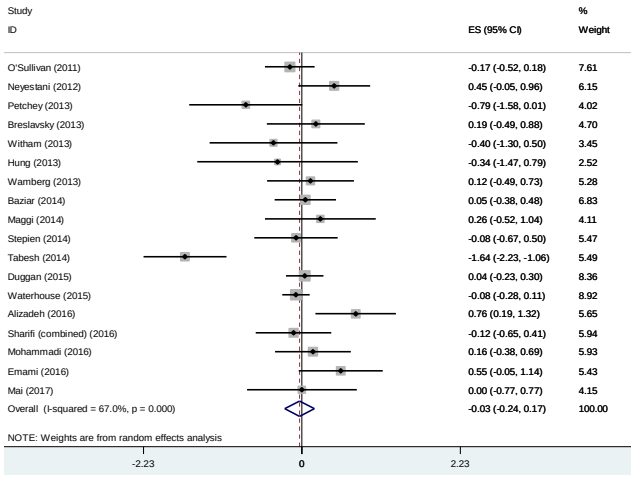


Figure 3. Forest plot of randomized controlled clinical trials illustrating standardized mean difference (Hedges' g) in serum adiponectin concentration change between the vitamin D supplementation and control groups for all eligible studies. The analysis was conducted using the random-effects model.

The effect of vitamin D supplementation on serum adiponectin levels

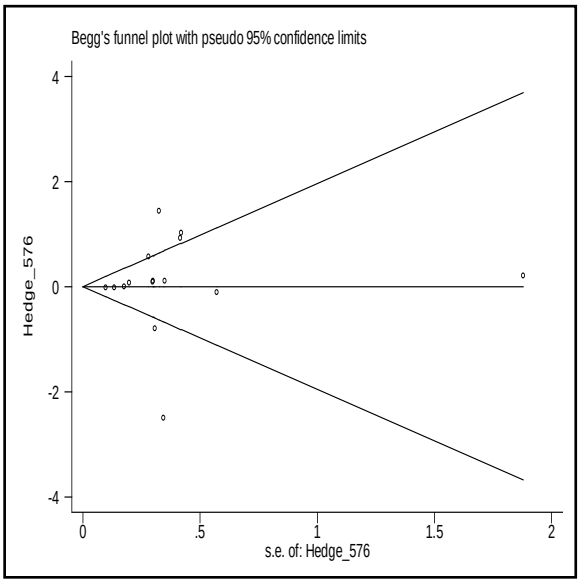
Eighteen clinical trials *[20-27, 31, 33-35, 41-46]* evaluated the effect of vitamin D supplementation on serum adiponectin. Meta-analysis could not find any significant effect of vitamin D supplement on serum adiponectin (Hedges' g = -0.034, 95 % CI: -0.243 to 0.174, p = 0.748) (**Figure 3**). There was a high level of heterogeneity between studies (Cochrane Q test, Q statistic = 51.44, P < 0.001, I_2 = 67.0%) (**Table 4**). Thus, several subgroup analyses were conducted to investigate the sources of heterogeneity. The non-significant effect of vitamin D supplementation on serum leptin levels was also shown across almost all subgroups. The results of this study were not impressed by using different correlation coefficients.

The analysis was conducted using a random-effects model.

Sensitivity analysis and publication bias

The sensitivity analysis could not show any substantial change according to the effect of vitamin D supplementation on leptin and adiponectin after one by one exclusion of the trials from the meta-analysis. Although a slight asymmetry was observed in Begg's funnel plots (**Figure 4A** for leptin and **Figure 4B** for adiponectin), there was no evidence of publication bias for meta-analyses evaluating the effect of vitamin D supplementation on leptin and adiponectin levels by using Beggs (P = 0.373, P = 0.820, respectively) and Egger's asymmetry tests (P=0.799, P = 0.932, respectively).

(A)



(B)

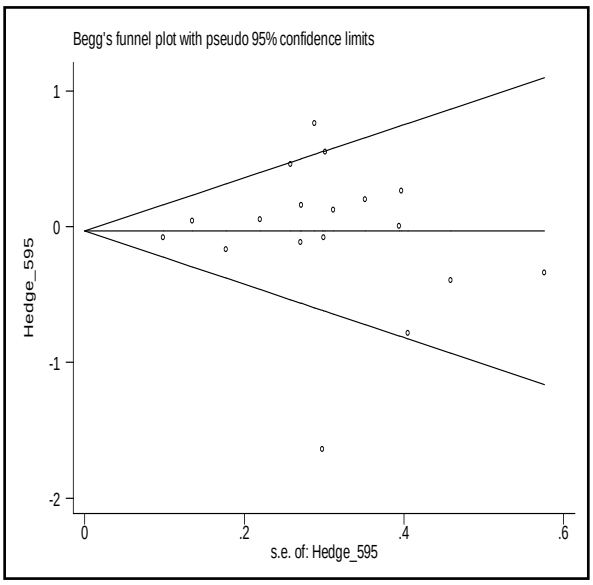


Figure 4. Begg's funnel plots (with pseudo 95% CIs) for the mean differences (MDs) versus their SEs (standard errors) for studies that assessed the effect of vitamin D supplementation on leptin (A) and adiponectin (B). The horizontal line shows the pooled standardized mean difference (Hedges' g) calculated with the DerSimonian and Laird random-effects model

Discussion

The present meta-analysis of twenty-two RCTs did not reveal any significant effects of vitamin D supplementation on circulating leptin and adiponectin levels. The subgroup analysis showed that vitamin D supplementation might significantly decrease serum leptin levels in patients with ESRD, and the current level of serum leptin increased following vitamin D supplementatiion in a single dose. Our findings are consistent with the results of a previous meta-analysis conducted by Dinca et al. *[28]*. However, they enrolled lower numbers of studies, including 9 RCTs, in their investigation. In contrast, the findings of the other meta-analysis by Hajimohammadi et al. *[29]* on 6 RCTs, who evaluated the effect of vitamin D supplementation only on leptin, showed a potential increase of serum leptin after vitamin D supplementation. That increase was dependent on the type of population, the dose of vitamin D supplementation, study duration, and the initial level of 25 (OH) D in the selected participants.

In comparison with a prior meta-analysis that conducted by Dinca et al. *[28]* and another study performed by Hajimohammadi et al. *[29]*, 13 and 16 more studies were found, respectively. Therefore, more subgroup analysis could be performed. The result of subgroup analysis based on the administered vitamin D dose between our study and the other meta-analyses conducted by Dinca et al. *[28]* is different. They did not report any significant effect of vitamin D supplementation on leptin when prescribed in a single dose comparing to multiple daily doses. Besides, there are some differences between our study and the other meta-analysis performed by Hajimohammadi et al. *[29]* in the findings of subgroup analysis based on being with or without diabetes, baseline level of 25 (OH) D and the study duration. They expressed that vitamin D supplementation could significantly increase the serum level of leptin in diabetic patients in comparison with others. Individuals with baseline 25 (OH) D < 30 ng/ml have significantly increased serum leptin following vitamin D supplementation compared to a subject who did not have vitamin D deficiency. Also, serum level of leptin significantly increased when study

duration reached a maximum of 12 months.

Adipokines usually are produced by adipose tissue *[49]* and numerous clinical studies have reported relationships between them and body composition indices *[50-52]*. Both adiponectin and leptin have a crucial role in energy homeostasis, and the regulation of adipose tissue *[53, 54]*. Leptin is a protein produced by the OB gene, so its concentration in people with obesity is higher than people with normal weight and is closely correlated with the percentage of body fat. Thus, the increase in body fat is translated into an increase in serum leptin and its possible mechanism is the induction of the OB gene expression as the subjects with obesity have a significantly greater amount of OB gene/mRNA level than normal-weight subjects *[55]*. In addition, adiponectin is another adipokine that its expression is reduced in the adipose tissue of obese subjects *[56]*. Adiponectin levels are higher in those without obesity compared to those with obesity *[57]*. According to significant metabolic effects of adiponectin like lowering glucose, enhancing fatty acid β-oxidation, and improving insulin sensitivity, it appears that hypoadiponectinemia is the result of obesity and adipose tissue-specific insulin resistance *[58]*. Therefore, weight changes and insulin are two of the most important regulators of adipokines *[59-62]*.

Vitamin D is an essential fat-soluble vitamin and its role in the pathogenesis of obesity is a subject of debate in clinical nutrition and public health *[63]*. Consequently, several studies have tried to examine the effect of vitamin D supplementation on obesity but the findings of meta-analyses of randomized controlled trials *[14-16]* did not indicate any beneficial effects of vitamin D supplementation on weight and body fat.

Insulin may also have a direct effect on adipokines regulation. Insulin reduces adiponectin levels in humans in vivo *[64, 65]* and in vitro *[66-68]*. Besides, diabetic patients have a greater amount of adiponectin in comparison with healthy controls (45). It seems that hyperinsulinemia may have a negative effect on circulating adiponectin levels and cause insulin resistance *[62]*. According to adiponectin role in glucose uptake and free fatty acid oxidation in muscles and inhibiting gluconeogenesis in the liver and improving insulin sensitivity, it appears that hypoadiponectinemia is a consequence of insulin resistance *[58, 69]*. Furthermore, there is a relationship between insulin resistance and serum leptin concentration in several studies *[61, 70, 71]*. Insulin resistant subjects have double leptin levels in comparison with those subjects who were not insulin resistant with the same degree of adiposity in both men and women *[72, 73]*. The results of the Miami Community Health Study revealed a significant inverse association between insulin resistance and leptin in both diabetic men and women, independent of obesity and hyperinsulinemia *[74]*. The mechanism of the relationship between insulin resistance, independent of adiposity, with elevated plasma leptin concentrations, might be the effect of elevated plasma insulin concentrations on stimulating OB gene expression *[75]*. However, meta-analyses indicated that there was insufficient evidence to suggest taking vitamin D for insulin improvement *[76-79]*. The possible mechanism of the lack of association between vitamin D and adipokines can be explained by the ineffectiveness of vitamin D supplementation on insulin level as modulator adipokines production.

The subgroup analysis based on vitamin D intervention amount revealed that a single dose of vitamin D supplementation can significantly increase serum leptin levels. Vitamin D probably stimulates the production of adipose leptin in a vitamin D receptor-dependent manner *[80]*. Results of a study done by Kong et al. *[80]* showed that serum leptin levels and adipose leptin mRNA transcript are significantly elevated after treatment with vitamin D. Maggi et al. *[20]* also observed that a single dose of 300,000 IU vitamin D3 could significantly increase

serum leptin level in diabetic patients after 24 weeks. Perhaps, the single large dose of vitamin D3 that was used in the included studies *[20, 27, 42]* was sufficient to increase 25OHD levels to the 75 nmol/L threshold that some investigators believe is required for beneficial health results *[81]*. Thus, serum leptin levels might increase.

Another result of the subgroup analysis based on kidney disease status showed that vitamin D supplementation significantly decreased serum leptin levels in participants with ESRD. Patients with ESRD have more vitamin D deficiency compared to the healthy population leading to an elevated morbidity and mortality rate in these patients. The serum levels of adipokines are generally elevated in these patients, and it is due to its decreased renal clearance *[55, 82]*. Several observational studies have reported an inverse association between vitamin D status and serum leptin levels *[83-86]*. According to the role of leptin in the development of inflammation, increasing the heart rate, blood pressure, and consequently increasing the risk of myocardial infarction (MI), and cerebrovascular accident, a decrease in serum leptin level might improve survival in ESRD patients *[33]*. In addition, some studies reported that the administration of active vitamin D increases insulin sensitivity in ESRD patients *[87-89]* that it may lead to a reduction in leptin serum level.

In the present study, more articles were found and included in comparison with two prior meta-analyses with the same search strategy, which is the strength of this meta-analysis. However, the present meta-analysis has several limitations, which must be noted. Various doses of vitamin D were administered for intervention in the involved studies, and the dose-response association between supplementation and adipokines changes could not be evaluated. The studies included were heterogeneous in the field of population similarities, including age, condition health, and serum level of vitamin D as well as study duration. Only published studies were used in this meta-analysis. The unpublished trials were not searched, and the researchers did not have access to individual patient-level data.

Conclusion

In conclusion, the present systematic review and meta-analysis of controlled clinical trials did not reveal a significant effect of vitamin D supplementation on adipokines concentration. However, subgroup analysis showed that vitamin D supplementation significantly increases the serum level of leptin when prescribed in a single mega-dose. Moreover, leptin levels significantly decreased in patients with ESRD after vitamin D supplementation. The long-term interventions with double-blind placebo-controlled design exploring the effect of single-dose administration of vitamin D and in patients with kidney disease are recommended to confirm our results.

Author's contribution

The authors' responsibilities were as follows— SJ and FJ conceived the study. SJ and SS carried out the literature search and data extraction. SJ conducted the quality of included studies, SJ and SS did the data analysis and interpretation. All authors contributed to the study conception, design, and drafting of the manuscript.

Conflict of interest

The authors have no potential financial or other conflicts of interest to declare.

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References

[1] Hawkes C. **Uneven dietary development: linking the policies and processes of globalization with the nutrition transition, obesity and diet-related chronic diseases**. *Globalization and health*. 2006;2:1

[2] Kelly T, Yang W, Chen C-S, Reynolds K, He J. **Global burden of obesity in 2005 and projections to 2030**.

International journal of obesity. 2008;32:1431

[3] Haslam D, James W. **Obesity. lancet 2005: 366; 1197--1209**. *International Journal of Advancements in Research & Technology*.1

[4] Berg AH, Scherer PE. **Adipose tissue, inflammation, and cardiovascular disease**. *Circulation research*. 2005;96:939-49

[5] Kelishadi R, Alikhani S, Delavari A, Alaedini F, Safaie A, Hojatzadeh E. **Obesity and associated lifestyle behaviours in Iran: findings from the first national non-communicable disease risk factor surveillance survey**. *Public health nutrition*. 2008;11:246-51

[6] Cao H. **Adipocytokines in obesity and metabolic disease**. *Journal of Endocrinology*. 2014;220:T47-T59

[7] De Pergola G, Silvestris F. **Obesity as a major risk factor for cancer**. *Journal of obesity*. 2013;2013

[8] Lubkowska A, Radecka A, Bryczkowska I, Rotter I, Laszczyńska M, Dudzińska W. **Serum adiponectin and leptin concentrations in relation to body fat distribution, hematological indices and lipid profile in humans**. *International journal of environmental research and public health*. 2015;12:11528-48

[9] Dastani Z, Hivert M-F, Timpson N, Perry JR, Yuan X, Scott RA, et al. **Novel loci for adiponectin levels and their influence on type 2 diabetes and metabolic traits: a multi-ethnic meta-analysis of 45,891 individuals**. *PLoS genetics*. 2012;8:e1002607

[10] Vaidya A, Williams JS, Forman JP. **The independent association between 25-hydroxyvitamin D and adiponectin and its relation with BMI in two large cohorts: the NHS and the HPFS**. *Obesity*. 2012;20:186-91

[11] Schwartz MW, Woods SC, Porte D, Seeley RJ, Baskin DG. **Central nervous system control of food intake**. *Nature*. 2000;404:661-71

[12] Troesch B, Hoeft B, McBurney M, Eggersdorfer M, Weber P. **Dietary surveys indicate vitamin intakes below recommendations are common in representative Western countries**. *British Journal of Nutrition*. 2012;108:692-8

[13] Saneei P, Salehi-Abargouei A, Esmaillzadeh A. **Serum 25-hydroxy vitamin D levels in relation to body mass index: a systematic review and meta-analysis**. *Obesity reviews : an official journal of the International Association for the Study of Obesity*. 2013;14:393-40410.1111/obr. 12016.

[14] Chandler PD, Wang L, Zhang X, Sesso HD, Moorthy MV, Obi O, et al. **Effect of vitamin D supplementation alone or with calcium on adiposity measures: a systematic review and meta-analysis of randomized controlled trials**. *Nutrition reviews*. 2015;73:577-93

[15] Pathak K, Soares M, Calton E, Zhao Y, Hallett J. **Vitamin D supplementation and body weight status: a systematic review and meta-analysis of randomized controlled trials**. *Obesity reviews*. 2014;15:528-37

[16] Mora N, Rieke K, Plitcha J, Segura A, Leehey D, DeShong K, et al. **25-Hydroxyvitamin D supplementation and BMI change: A meta-analysis of randomized controlled trials**. *Journal of obesity & weight loss therapy*. 2013;3:181

[17] Bellia A, Garcovich C, D'Adamo M, Lombardo M, Tesauro M, Donadel G, et al. **Serum 25-hydroxyvitamin D levels are inversely associated with systemic inflammation in severe obese subjects**. *Internal and emergency medicine*. 2013;8:33-40

[18] Husemoen L, Skaaby T, Martinussen T, Jørgensen T, Thuesen B, Kistorp C, et al. **Investigating the causal effect of vitamin D on serum adiponectin using a mendelian randomization approach**. *European journal of clinical nutrition*. 2014;68:189-95

[19] Ghavamzadeh S, Mobasseri M, Mahdavi R. **The Effect of Vitamin D Supplementation on Adiposity, Blood Glycated Hemoglobin, Serum Leptin and Tumor Necrosis Factor-alpha in Type 2 Diabetic Patients**. *International journal of preventive medicine*. 2014;5:1091-8

[20] Maggi S, Siviero P, Brocco E, Albertin M, Romanato G, Crepaldi G. **Vitamin D deficiency, serum leptin and osteoprotegerin levels in older diabetic patients: an input to new research avenues**. *Acta diabetologica*. 2014; 51:461-910.1007/s00592-013-0540-4.

[21] Petchey WG, Hickman IJ, Prins JB, Hawley CM, Johnson DW, Isbel NM. **Vitamin D does not improve the metabolic health of patients with chronic kidney disease stage 3–4: a randomized controlled trial**. *Nephrology*. 2013;18:26-35

[22] Tabesh M, Azadbakht L, Faghihimani E, Tabesh M, Esmaillzadeh A. **Calcium-vitamin D cosupplementation influences circulating inflammatory biomarkers and adipocytokines in vitamin D-insufficient diabetics: a randomized controlled clinical trial**. *J Clin Endocrinol Metab*. 2014;99:E2485-9310.1210/jc. 2014-1977.

[23] Alizadeh N, Khalili H, Mohammadi M, Abdollahi A, Ala S. **Effect of vitamin D on stress-induced hyperglycaemia and insulin resistance in critically ill patients**. *Int J Clin Pract*. 2016;70:396-40510.1111/ijcp.12795.

[24] Neyestani TR, Nikooyeh B, Alavi-Majd H, Shariatzadeh N, Kalayi A, Tayebinejad N, et al. **Improvement of vitamin D status via daily intake of fortified yogurt drink either with or without extra calcium ameliorates systemic inflammatory biomarkers, including adipokines, in the subjects with type 2 diabetes**. *J Clin Endocrinol Metab*. 2012;97:2005-1110.1210/jc.2011-3465.

[25] Hung AM, Sundell MB, Plotnikova NE, Bian A, Shintani A, Ellis CD, et al. **A Pilot Study of Active Vitamin D Administration and Insulin Resistance in African American Patients Undergoing Chronic Hemodialysis**. *Journal of Renal Nutrition*. 2013;23: 185-9310.1053/j.jrn. 2012. 06.005.

[26] O'Sullivan A, Gibney MJ, Connor AO, Mion B, Kaluskar S, Cashman KD, et al. **Biochemical and metabolomic phenotyping in the identification of a vitamin D responsive metabotype for markers of the metabolic syndrome**. *Molecular nutrition & food research*. 2011;55:679-9010.1002/mnfr.201000458.

[27] Witham MD, Adams F, Kabir G, Kennedy G, Belch JJ, Khan F. **Effect of short-term vitamin D supplementation on markers of vascular health in South Asian women living in the UK--a randomised controlled trial**. *Atherosclerosis*. 2013;230:293-910.1016/j.atherosclerosis.2013.08.005.

[28] Dinca M, Serban M-C, Sahebkar A, Mikhailidis DP, Toth PP, Martin SS, et al. **Does vitamin D supplementation alter plasma adipokines concentrations? A systematic review and meta-analysis of randomized controlled trials**. *Pharmacological research*. 2016;107:360-71

[29] Hajimohammadi M, Shab-Bidar S, Neyestani T. **Vitamin D and serum leptin: A systematic review and meta-analysis of observational studies and randomized controlled trials**. *European journal of clinical nutrition*. 2017;71:1144-53

[30] Higgins JP, Green S. **Cochrane handbook for systematic reviews of interventions**: *John Wiley & Sons*; 2011

[31] Breslavsky A, Frand J, Matas Z, Boaz M, Barnea Z, Shargorodsky M. **Effect of high doses of vitamin D on arterial properties, adiponectin, leptin and glucose homeostasis in type 2 diabetic patients**. *Clinical nutrition (Edinburgh, Scotland)*. 2013;32:970-510.1016/j.clnu.2013.01.020.

[32] Hajimohammadi M, Shab-Bidar S, Neyestani TR. **Consumption of vitamin D-fortified yogurt drink increased leptin and ghrelin levels but reduced leptin to ghrelin ratio in type 2 diabetes patients: a single blind randomized controlled trial**. *European journal of nutrition*. 2017:1-810.1007/s00394-017-1397-z.

[33] Naini AE, Vahdat S, Hedaiati ZP, Shahzeidi S, Pezeshki AH, Nasri H. **The effect of vitamin D administration on serum leptin and adiponectin levels in end-stage renal disease patients on hemodialysis with vitamin D deficiency: A placebo-controlled double-blind clinical trial**. *Journal of Research in Medical Sciences*. 2016;21:1

[34] Baziar N, Jafarian K, Shadman Z, Qorbani M, Khoshniat Nikoo M, Abd Mishani M. **Effect of therapeutic dose of vitamin d on serum adiponectin and glycemia in vitamin d-insufficient or deficient type 2 diabetic patients**. *Iranian Red Crescent medical journal*. 2014;16:e2145810.5812/ ircmj. 21458.

[35] Sharifi N, Amani R, Hajiani E, Cheraghian B. **Women may respond different from men to vitamin D supplementation regarding cardiometabolic biomarkers**. *Experimental biology and medicine (Maywood, NJ)*. 2016;241:830-810.1177/ 1535370216629009.

[36] Higgins J, Thompson SG. **Quantifying heterogeneity in a meta-analysis**. *Statistics in medicine*. 2002;21:1539-58

[37] Egger M, Davey-Smith G, Altman D. **Systematic reviews in health care: meta-analysis in context**: *John Wiley & Sons*; 2008

[38] Egger M, Smith GD, Schneider M, Minder C. **Bias in meta-analysis detected by a simple, graphical test**. *Bmj*. 1997;315:629-34

[39] Sterne JA, Egger M, Smith GD. **Systematic reviews in health care: Investigating and dealing with publication and other biases in meta-analysis**. *BMJ: British Medical Journal*. 2001;323:101

[40] Al-Sofiani ME, Jammah A, Racz M, Khawaja RA, Hasanato R, El-Fawal HA, et al. **Effect of Vitamin D Supplementation on Glucose Control and Inflammatory Response in Type II Diabetes: A Double Blind, Randomized Clinical Trial**. *International journal of endocrinology and metabolism*. 2015; 13: e2260410.5812/ ijem. 22604.

[41] Duggan C, de Dieu Tapsoba J, Mason C, Imayama I, Korde L, Wang CY, et al. **Effect of Vitamin D3 Supplementation in Combination with Weight Loss on Inflammatory Biomarkers in Postmenopausal Women: A Randomized Controlled Trial**. *Cancer prevention research (Philadelphia, Pa)*. 2015;8:628-3510.1158/1940-6207.capr-14-0449.

[42] Mai S, Walker GE, Vietti R, Cattaldo S, Mele C, Priano L, et al. **Acute vitamin D3 supplementation in severe obesity: Evaluation of multimeric adiponectin**. *Nutrients*. 2017;910.3390/nu9050459.

[43] Mohammadi SM, Eghbali SA, Soheilikhah S, Ashkezari SJ, Salami M, Afkhami-Ardekani M, et al. **The effects of vitamin D supplementation on adiponectin level and insulin resistance in first-degree relatives of subjects with type 2 diabetes: a randomized double-blinded controlled trial**. *Electronic Physician*. 2016;8:2849

[44] Stepien M, O'Mahony L, O'Sullivan A, Collier J, Fraser WD, Gibney MJ, et al. **Effect of supplementation with vitamin D 2-enhanced mushrooms on vitamin D status in healthy adults**. *Journal of nutritional science*. 2013;2

[45] Wamberg L, Cullberg KB, Rejnmark L, Richelsen B, Pedersen SB. **Investigations of the anti-inflammatory effects of vitamin D in adipose tissue: results from an in vitro study and a randomized controlled trial**. *Hormone and metabolic research = Hormon- und Stoffwechselforschung = Hormones et metabolisme*. 2013; 45: 456-6210. 1055/ s-0032-1331746.

[46] Waterhouse M, Tran B, Ebeling PR, English DR, Lucas RM, Venn AJ, et al. **Effect of vitamin D supplementation on selected inflammatory biomarkers in older adults: a secondary analysis of data from a randomised, placebo-controlled trial**. *The British journal of nutrition*. 2015;114:693-910. 1017/s0007114515002366.

[47] Chai W, Bostick RM, Ahearn TU, Franke AA, Custer LJ, Cooney RV. **Effects of vitamin D3 and calcium supplementation on serum levels of tocopherols, retinol, and specific vitamin D metabolites**. *Nutrition and cancer*. 2012;64:57-6410.1080/ 01635581.2012. 630552.

[48] Tarcin O, Yavuz DG, Ozben B, Telli A, Ogunc AV, Yuksel M, et al. **Effect of vitamin D deficiency and replacement on endothelial function in asymptomatic subjects**. *J Clin Endocrinol Metab*. 2009;94:4023-3010.1210/jc.2008-1212.

[49] Al Mutairi S, Mojiminiyi OA, Al Alawi A, Al Rammah T, Abdella N. **Study of leptin and adiponectin as disease markers in subjects with obstructive sleep apnea**. *Disease markers*. 2014;2014

[50] Hsieh C-J, Wang P-W, Chen T-Y. **The relationship between regional abdominal fat distribution and both insulin resistance and subclinical chronic inflammation in non-diabetic adults**. *Diabetology & metabolic syndrome*. 2014;6:49

[51] Suyila Q, Cui H, Yang L, Zhao L, Zhang R, Su X. **Serum leptin concentrations in Mongolian women**. *Obesity research & clinical practice*. 2013;7:e75-e80

[52] Zhao YN, Li Q, Li YC. **Effects of body mass index and body fat percentage on gestational complications and outcomes**. *Journal of Obstetrics and Gynaecology Research*. 2014;40:705-10

[53] Forsythe LP, Kent EE, Weaver KE, Buchanan N, Hawkins NA, Rodriguez JL, et al. **Receipt of psychosocial care among cancer survivors in the United States**. *Journal of Clinical Oncology*. 2013;31:1961-9

[54] Ganz PA. **Survivorship: adult cancer survivors**. *Primary Care: Clinics in Office Practice*. 2009;36:721-41

[55] Considine RV, Sinha MK, Heiman ML, Kriauciunas A, Stephens TW, Nyce MR, et al. **Serum immunoreactive-leptin concentrations in normal-weight and obese humans**. *New England Journal of Medicine*. 1996;334:292-5

[56] Tarquini R, Lazzeri C, Laffi G, Gensini G. **Adiponectin and the cardiovascular system: from risk to disease**. *Internal and emergency medicine*. 2007;2:165-76

[57] Scaglione R, Di Chiara T, Cariello T, Licata G. **Visceral obesity and metabolic syndrome: two faces of the same medal?** *Internal and emergency medicine*. 2010;5:111-9

[58] Duncan BB, Schmidt MI, Pankow JS, Bang H, Couper D, Ballantyne CM, et al. **Adiponectin and the development of type 2 diabetes**. *Diabetes*. 2004; 53:2473-8

[59] Halberg N, Wernstedt-Asterholm I, Scherer PE. **The adipocyte as an endocrine cell**. *Endocrinology and Metabolism Clinics*. 2008;37:753-68

[60] Hauner H. **Secretory factors from human adipose tissue and their functional role**. *Proceedings of the Nutrition Society*. 2005;64:163-9

[61] Mente A, Razak F, Blankenberg S, Vuksan V, Davis AD, Miller R, et al. **Ethnic variation in adiponectin and leptin levels and their association with adiposity and insulin resistance**. *Diabetes care*. 2010;33:1629-34

[62] Trujillo M, Scherer P. **Adiponectin–journey from an adipocyte secretory protein to biomarker of the metabolic syndrome**. *Journal of internal medicine*. 2005;257:167-75

[63] Van Schoor NM, Lips P. **Worldwide vitamin D status**. *Best practice & research Clinical endocrinology & metabolism*. 2011;25:671-80

[64] Combs TP, Berg AH, Obici S, Scherer PE, Rossetti L. **Endogenous glucose production is inhibited by the adipose-derived protein Acrp30**. *Journal of Clinical Investigation*. 2001;108:1875

[65] Joseph GY, Javorschi S, Hevener AL, Kruszynska YT, Norman RA, Sinha M, et al. **The effect of thiazolidinediones on plasma adiponectin levels in normal, obese, and type 2 diabetic subjects**. *Diabetes*. 2002;51:2968-74

[66] Fasshauer M, Klein J, Neumann S, Eszlinger M, Paschke R. **Hormonal regulation of adiponectin gene expression in 3T3-L1 adipocytes**. *Biochemical and biophysical research communications*. 2002;290:1084-9

[67] Halleux C, Takahashi M, Delporte M, Detry R, Funahashi T, Matsuzawa Y, et al. **Secretion of adiponectin and regulation of apM1 gene expression in human visceral adipose tissue**. *Biochemical and biophysical research communications*. 2001;288:1102-7

[68] Motoshima H, Wu X, Sinha MK, Hardy VE, Rosato EL, Barbot DJ, et al. **Differential regulation of adiponectin secretion from cultured human omental and subcutaneous adipocytes: effects of insulin and rosiglitazone**. *The Journal of Clinical Endocrinology &*

Metabolism. 2002;87:5662-7

[69] Di Chiara T, Argano C, Corrao S, Scaglione R, Licata G. **Hypoadiponectinemia: a link between visceral obesity and metabolic syndrome**. *Journal of nutrition and metabolism*. 2011;2012

[70] Esteghamati A, Khalilzadeh O, Anvari M, Rashidi A, Mokhtari M, Nakhjavani M. **Association of Serum Leptin Levels With Homeostasis Model Assessment–Estimated Insulin Resistance and Metabolic Syndrome: The Key Role of Central Obesity**. *Metabolic syndrome and related disorders*. 2009;7:447-52

[71] Huang K, Lin R, Kormas N, Lee L, Chen C, Gill T, et al. **Plasma leptin is associated with insulin resistance independent of age, body mass index, fat mass, lipids, and pubertal development in nondiabetic adolescents**. *International journal of obesity*. 2004;28:470-5

[72] Zuo H, Shi Z, Yuan B, Dai Y, Wu G, Hussain A. **Association between serum leptin concentrations and insulin resistance: a population-based study from China**. *PLoS One*. 2013;8:e54615

[73] Nakhjavani M, Esteghamati A, Tarafdari AM, Nikzamir A, Ashraf H, Abbasi M. **Association of plasma leptin levels and insulin resistance in diabetic women: a cross-sectional analysis in an Iranian population with different results in men and women**. *Gynecological Endocrinology*. 2011;27:14-9

[74] Donahue RP, Prineas RJ, Donahue RD, Zimmet P, Bean JA, De Courten M, et al. **Is fasting leptin associated with insulin resistance among nondiabetic individuals? The Miami Community Health Study**. *Diabetes care*. 1999;22:1092-6

[75] Segal KR, Landt M, Klein S. **Relationship between insulin sensitivity and plasma leptin concentration in lean and obese men**. *Diabetes*. 1996;45:988-91

[76] Autier P, Boniol M, Pizot C, Mullie P. **Vitamin D status and ill health: a systematic review**. *The lancet Diabetes & endocrinology*. 2014;2:76-89

[77] George P, Pearson E, Witham M. **Effect of vitamin D supplementation on glycaemic control and insulin resistance: a systematic review and meta-analysis**. *Diabetic Medicine*. 2012;29

[78] Mitri J, Muraru M, Pittas A. **Vitamin D and type 2 diabetes: a systematic review**. *European journal of clinical nutrition*. 2011;65:1005-15

[79] Seida JC, Mitri J, Colmers IN, Majumdar SR, Davidson MB, Edwards AL, et al. **Clinical review: effect of vitamin D3 supplementation on improving glucose homeostasis and preventing diabetes: a systematic review and meta-analysis**. *The Journal of clinical endocrinology and metabolism*. 2014;99:3551

[80] Kong J, Chen Y, Zhu G, Zhao Q, Li YC. **1, 25-Dihydroxyvitamin D3 upregulates leptin expression in mouse adipose tissue**. *Journal of Endocrinology*. 2013;216:265-71

[81] Bischoff-Ferrari HA, Giovannucci E, Willett WC, Dietrich T, Dawson-Hughes B. **Estimation of optimal serum concentrations of 25-hydroxyvitamin D for multiple health outcomes**. *The American journal of clinical nutrition*. 2006;84:18-28

[82] Huang J-W, Yen C-J, Chiang H-W, Hung K-Y, Tsai T-J, Wu K-D. **Adiponectin in peritoneal dialysis patients: a comparison with hemodialysis patients and subjects with normal renal function**. *American Journal of Kidney Diseases*. 2004;43:1047-55

[83] Ghaderian SB, Beladi-Mousavi SS. **The role of diabetes mellitus and hypertension in chronic kidney disease**. *Journal of renal injury prevention*. 2014;3:109

[84] Nasri H, Ardalan M-R, Rafieian-Kopaei R. **On the occasion of world hypertension day 2014**. *J Parathyr Dis*. 2014;2:5-6

[85] Rafieian-Kopaei M, Nasri H. **Association of serum lipids with levels of leptin in hemodialysis patients**. *Journal of Nephropharmacology*. 2013;2:17

[86] Rastegari E, Nasri H. **Association of serum leptin with serum C-reactive protein in hemodialysis patients**. *Journal of Nephropharmacology*. 2012;1:19

[87] Bonakdaran S, Ayatollahi H, Mojahedi MJ, Sharifipoor F, Shakeri M. **Impact of treatment with oral calcitriol on glucose intolerance and dyslipidemia (s) in hemodialysis patients**. *Saudi Journal of Kidney Diseases and Transplantation*. 2008;19:942

[88] Khajehdehi P, Taheri S. **Effect of oral calcitriol pulse therapy on the lipid, calcium, and glucose homeostasis of hemodialysis-patients: its safety in a combination with oral calcium carbonate**. *Journal of Renal Nutrition*. 2003; 13:78-83

[89] Stróżecki P, Kretowicz M, Odrowąż-Sypniewska G, Manitius J. **The influence of intravenous 1, 25 (OH) 2D3 therapy on glucose metabolism in hemodialyzed patients with secondary hyperparathyroidism**. *Renal failure*. 2004;26:345-8.