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Review

Effect of calcium and vitamin D co-supplementation on lipid profile of overweight/obese subjects: A systematic review and meta-analysis of the randomized clinical trials

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ABSTRACT

Background: Results of the studies assessed the effect of calcium and vitamin D co-supplementation on lipid profiles are contradictory. Due to the inconsistent results found in the literature, we performed a systematic review and meta-analysis of randomized clinical trials (RCTs) to assess the effect of calcium and vitamin D co-supplementation on lipids concentrations.

Methods: A systematic search was carried out in Web of Science, PubMed, Scopus and Cochrane library without any language and time restriction up to March 2019, to retrieve the randomized controlled trials (RCTs) which examined the effect of calcium and vitamin D co-supplementation on lipids concentrations in overweight/obese subjects. Meta-analyses were carried out using a random effects model. I2 index was used to evaluate the heterogeneity.

Results: Initial search yielded 1847 publications. Seven RCTs with 414 patients were eligible. Results show that lower doses of vitamin D and calcium significantly reduced TG and TC levels. Furthermore, we found that this co-supplementation increased the blood concentrations of HDL-C. The effect of calcium and vitamin D co-supplementation on increasing HDL-C was significant in equal or less than 8 weeks supplementation and in higher doses of vitamin D and calcium. In addition, we found that this co-supplementation significantly reduced LDL-C in equal or less than 8 weeks supplementation.

Conclusion: Present systematic review and meta-analysis indicated the beneficial effects of calcium and vitamin D co-supplementation on lipid profile of overweight/obese subjects. We found that the lower doses and short-term supplementation could have more beneficial effects.

1. Introduction

Recently, it has been shown that in overweight people with low calcium and dairy consumption, the risk of developing a metabolic syndrome was much higher than those who were overweight, but had higher calcium and dairy consumption (Pereira et al., 2002). This findings suggest that adequate calcium intake, as well as having a healthy diet and adequate physical activity, can have a significant effect on the predisposition to a healthier metabolic profile (Eriksson and Lindgarde, 1991). From a physiological point of view, the metabolic syndrome and its potential relationship with calcium or dairy consumption are the focus of attention recently. Previous studies have shown that a low calcium diet increases the calcium content of the adipocyte (Zemel et al., 2000). One of the consequences of increasing levels of calcium in the adipose tissue is the increase in lipogenesis, which can explain the results of previous studies that demonstrated the relationship between low calcium intake and low lipid oxidation (Melanson et al., 2003). These findings were confirmed by the studies that indicated a relationship between calcium intake and lipoprotein levels. It has been reported that low calcium intake was associated with increased levels of low-density lipoprotein (LDL) and a reduction in high-density lipoprotein (HDL) levels (Jacqmain et al., 2003). As well as calcium, the association of vitamin D with metabolic syndrome has been also well-defined. Several studies have shown that vitamin D plays

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an important role in reducing the risk factors associated with cardiovascular disease such as dyslipidemia (Ganji et al., 2011; Anagnostis et al., 2010). It has been shown that serum concentrations of vitamin D were inversely associated with total cholesterol (TC), LDL and triglyceride (TG) (Glueck et al., 2016).

Considering the synergistic effects of calcium and vitamin D, several studies have investigated the effect of combined vitamin D and calcium supplementation on lipid profile (Samimi et al., 2016; Major et al., 2007). However, the results of these studies are contradictory. Major et al., reported that vitamin D and calcium co-supplementation significantly reduced the LDL levels, whereas, it had no significant effect on TG or TC (Major et al., 2007). Another study indicated that this co-supplementation had a significant effect in increasing the HDL levels, whereas, no significant reduction was observed in TG, LDL and TC levels (Samimi et al., 2016). Due to the inconsistent results found in the literature, we performed a systematic review and meta-analysis of randomized clinical trials (RCTs) to assess the effect of calcium and vitamin D co-supplementation on lipids concentrations.

2. Methods

2.1. Search strategy and study selection

The present study was performed according to PRISMA guidelines (Moher et al., 2009). The systematic search of literature was performed independently by two authors (OA and SK) in PubMed, Scopus, Cochrane's library and ISI Web of Science databases up to March 2019, with the following keywords in titles, abstracts and keywords: “calcium” and “vitamin D or cholecalciferol or ergocalciferol or alphacalcidol or alfacalcidol or calcitriol or paricalcitol or doxercalciferol or vitamin D2 or vitamin D3” and “triglyceride or Triacylglycerol or cholesterol or Lipoprotein or very low density lipoprotein or VLDL or low density lipoprotein or LDL or LDL-C or high density lipoprotein or HDL or HDL-C or lipid” in combination with “Intervention or controlled trial or randomized or randomized or random or randomly or placebo or assignment or clinical trial or Trial”. There was no language or time restriction. Finally, the systematic search was completed by the reference list check of the qualified articles.

2.2. Inclusion and exclusion criteria

The inclusion criteria was as follows: 1) Randomized controlled clinical trials of oral co-supplementation of calcium and vitamin D with a control group; 2) Trials with duration of more than one week; and 3) Trials in which the blood concentrations of TC, LDL-C, HDL-C, VLDL and TG was reported at baseline and at the end of the supplementation in both the control and intervention groups with SD, SEM, or CI 95%; 4) Trials in which co-supplementation of calcium and vitamin D was not combined with other vitamins and minerals; 5) Trials in which the age of participants was ≥18 years old, and the mean body mass index (BMI) was ≥27 kg/m^2. Studies were excluded if were animal-based studies, reviews, posters and letters to editors.

2.3. Data extraction and quality assessment

After removing repeated studies, two authors (OA and SK) separately reviewed the title and abstract of the articles to find relevant studies. The full text of the studies was reviewed to determine eligibility. Jadad score is used to determine the quality of studies based on, randomness, blindness and the reasons of dropouts (Jadad et al., 1996). Characteristics of the included studies were extracted using a form containing the following items of first author's name, publication year, study design, country, sample size in intervention and control groups, duration and dosage of calcium and vitamin D supplementation, participants sex, mean age and BMI, and baseline and final lipid profile concentrations in control and treatment groups.

2.4. Data synthesis and statistical analysis

Before analysis of the data, the lipid levels in mmol/L were converted to mg/dl. The mean changes (mean values ± standard deviation) in the TC, HDL-C, LDL-C, VLDL-C and TG for each study were calculated. Standard errors were converted to the standard deviation (SDs) for the analyses, by following formula: $SD = SE \times \sqrt{n}$ (n = sample size in each group). SDs of the mean difference were calculated by using the following formula: SD = square root [$(SD_{baseline})$^2 + (SD_{final})^2 − (2R × $SD_{baseline}$ × SD_{final})], assuming a correlation coefficient (R) = 0.8 (Borenstein et al., 2009). All analyses were conducted using STATA v.12 (Stata Corporation, College Station, TX, USA). Heterogeneity was tested using the I^2 statistic, and an I^2 value ≥ 50% with a level of significance of $P < 0.05$ by the Cochran Q-test was interpreted as evidence of substantial heterogeneity. To determine potential publication bias, the egger's test and funnel plots for each result were examined.

3. Results

3.1. Search results and study selection

A total number of 1847 studies were found in the first step of literature search in PubMed, Scopus, Cochrane's library and ISI Web of Science databases. After removal of duplicated studies, 1455 studies were included for the title and abstract screening. Then, 1443 studies (125 animal studies, 50 review studies and 1268 non related studies) were excluded since they did not meet inclusion criteria. Finally, of 12 studies which were found eligible for full text evaluation, 2 studies were excluded due to lack of enough data, and 3 studies were excluded because these studies were not conducted on overweight or obese subjects. Therefore, 7 studies were included (Major et al., 2007; Asemi et al. 2012, 2015; Asemi et al., 2014; Gagnon et al., 2014; Tabesh et al., 2014; Samimi et al., 2016). All the included studies were randomized and controlled trials. Process of the study selection is shown in the flow diagram (Fig. 1).

3.2. Study characteristics

The included trials were carried out from 2007 to 2017. One study was conducted in Canada (Major et al., 2007), one study was in Germany (Gagnon et al., 2014), and five studies were in Iran (Asemi et al. 2012, 2015; Asemi et al., 2014; Tabesh et al., 2014; Samimi et al., 2016). The participants in the intervention arm were 200 subjects and in the control arm were 214 subjects with the age range of 24.3–53.8 years old. The range of BMI was 25.6–31.3 kg/m^2. All the studies were parallel in designed. Trial duration was between 6 and 24 weeks. Dosage of the co-supplementation varied from 500 to 1200 mg/day for calcium and 200 IU per day to 50000 IU per week for vitamin D. The type of calcium administered in all the studies was calcium carbonate (Major et al., 2007; Asemi et al. 2012, 2015; Asemi et al., 2014; Gagnon et al., 2014; Tabesh et al., 2014; Samimi et al., 2016). The type of vitamin D used in all the studies was vitamin D3 (Major et al., 2007; Asemi et al. 2012, 2015; Asemi et al., 2014; Gagnon et al., 2014; Tabesh et al., 2014; Samimi et al., 2016) (see Table 1).

3.3. Meta-analysis

3.3.1. Effect of calcium and vitamin D co-supplementation on TG

The impact of calcium and vitamin D co-supplementation on TG levels was assessed in 7 effects size (Major et al., 2007; Asemi et al. 2012, 2015; Asemi et al., 2014; Gagnon et al., 2014; Tabesh et al., 2014; Samimi et al., 2016). Pooled analysis showed no significant reduction in TG following calcium and vitamin D co-supplementation (weighted mean differences (WMD): -13.85 mg/dl; 95% CI:-31.00 to 3.30; $p = 0.113$) (Fig. 2). Between-studies heterogeneity was significant

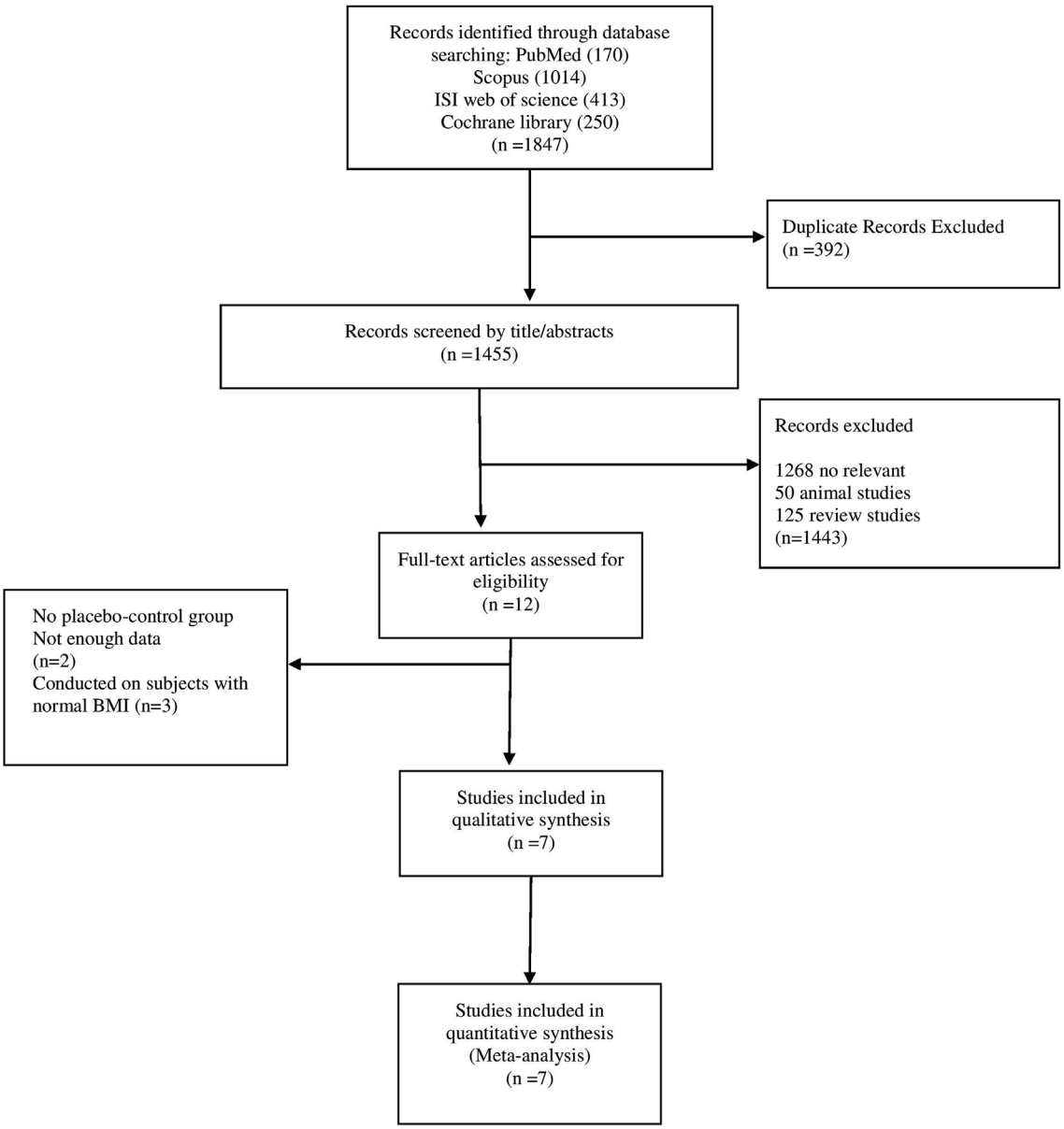

Fig. 1. Flow diagram of the literature search.

(I^2 = 79.0%, $p < 0.001$). There was no significant change in TG levels in any of the subgroups except for the subgroup of vitamin D and calcium co-supplementation dose. According to the results, lower doses of the vitamin D and calcium significantly reduced TG levels. Based on egger's test there was no publication bias ($p = 0.089$).

3.3.2. Effect of calcium and vitamin D co-supplementation on TC

Calcium and vitamin D co-supplementation had no significant effect on TC concentrations (−10.04 mg/dl, 95% CI: -36.58 to 16.50; $p = 0.458$) (Fig. 3). There was a significant evidence of heterogeneity between trials (I^2 = 97.4%, $p < 0.001$). As Table 2 shows, lower doses of the calcium and vitamin D co-supplementation resulted in a significant reduction in TC concentration. Egger's test demonstrated that, there was a bias in publications ($p < 0.001$).

3.3.3. Effect of calcium and vitamin D co-supplementation on HDL-C

Pooled effect size of 7 trials showed that co-supplementation of calcium and vitamin D had a significant effect on HDL-C (3.91 mg/dl; 95% CI: 0.38 to 7.45; $p = 0.03$)(Fig. 4). There was a significant heterogeneity between studies (I2 = 84.5%, $p < 0.001$). According to the subgroup analysis calcium and vitamin D co-supplementation significantly increased the blood concentrations of HDL-C in subgroups of equal and less than 8 weeks supplementation duration and in higher doses (≥2000 IU/day for vitamin D and ≥1000 mg for calcium). The publication bias was significant ($p < 0.001$).

3.3.4. Effect of calcium and vitamin D co-supplementation on LDL-C

Calcium and vitamin D co-supplementation had no significant effect on LDL-C levels (−5.35 mg/dl, 95% CI: -14.66 to 3.96; $p = 0.260$) (Fig. 5). Between-studies heterogeneity was significant (I2 = 84.4%, $p < 0.001$). Results of the subgroup analysis indicated that this co-supplementation had significant effect on LDL-C in supplementation duration equal or less than 8 weeks. The publication bias was significant ($p = 0.001$).

4. Discussion

This meta-analysis is the first to report that, in overweight or obese

Table 1
Characteristic of included studies in meta-analysis dies in meta-analysis.

Author	year	country	Study design	participant	sex	Mean age (intervention/ control)	Mean BMI (intervention/ control)	Trial duration (week)	Daily dose of Calcium (mg)	type of Calcium	Daily dose of vitamin D (IU)	type of vitamin D	Sample size (intervention/control)	Jadad score
GC Major	2007	Canada	R/DB/PL	overweight or obese	F	43.6/41.6	31.4/32.3	15	600	calcium carbonate	200 daily	vitamin D3	30/33	4
Z Asemi	2012	IRAN	R/SB/PL	pregnant	F	NR/NR	28.5/26.7	9	500	calcium carbonate	200 daily	vitamin D3	24/25	3
Z Asemi	2014	IRAN	R/DB/PL	GDM	F	28/30	29/30.5	6	1000	calcium carbonate	50,000 U twice during the study	vitamin D3	28/28	5
M Tabesh	2014	IRAN	R/DB/PL	type 2 diabetes	F/M	49.8/51	29.9.30.3	8	1000	calcium carbonate	50000 per week	vitamin D3	30/30	4
C Gagnon	2014	Germany	R/DB/PL	at risk for Type 2 Diabetes	F/M	53.8/55.3	31.1/31.9	24	1200	calcium lactate	2000-6000 daily	vitamin D3	32/42	5
Z Asemi	2014	IRAN	R/DB/PL	polycystic ovary syndrome	F	24.9/24.3	28.3/27.5	8	1000	calcium carbonate	50000 per week	vitamin D3	26/26	5
M Samimi	2015	IRAN	R/DB/PL	pregnant	F	27.3/27.1	27.4/25.6	12	1000	calcium carbonate	50000 per 2 weeks	vitamin D3	30/30	5

Abbreviations: DB, double-blinded; PC, placebo-controlled; R, randomized; NR, not reported; F, Female; M, Male.

subjects, supplementation with calcium and vitamin D improved blood lipid. We found that lower doses of vitamin D and calcium significantly reduced TG and TC levels. Furthermore, we found that this co-supplementation increased the blood concentrations of HDL-C. The effect of calcium and vitamin D co-supplementation on increasing HDL-C was significant in equal or less than 8 weeks supplementation and in higher doses of vitamin D and calcium. In addition, we found that this co-supplementation significantly reduced LDL-C in equal or less than 8 weeks supplementation.

The beneficial effects of calcium on reducing lipid and lipoprotein concentrations can be explained by several mechanisms which include reducing the absorption of fatty acids and increasing the excretion of fatty acids via feces, which is the result of the formation of insoluble calcium-fatty soaps in the gut (Denke et al., 1993; Reid, 2004). Such a decrease in fat absorption, especially in saturated fat, can reduce blood concentrations of both TC and LDL-C (Vaskonen, 2003). Other properties related to calcium are the ability to bind bile acids, increase the cholesterol conversion to bile acids, and thus, increase the excretion of cholesterol (Van der Meer et al., 1990; Vaskonen et al., 2002). In addition, it has been shown that increased intracellular calcium in hepatocytes can trigger microsomal triacylglycerol transfer protein (MTP), which is involved in the synthesis and excretion of VLDL from hepatocytes (Cho et al., 2005). In the case of low dietary intake of calcium, calcitrophic hormones increase the calcium uptake by adipocyte cells, and thus, an increase in calcium intake leads to the reduction of intracellular calcium in adipocytes, which consequently leads to increased lipolysis (Melanson et al., 2005; Zemel et al., 2000). Therefore, it can be assumed that with increasing calcium intake, the concentrations of calcium in hepatocytes are reduced, resulting in a decrease in the synthesis of VLDL and LDL (Melanson et al., 2005). In addition, increasing calcium intake increases the lipids mobilization, which ultimately increases the oxidation of lipids (Melanson et al., 2003). Although, the mechanism of the effects of calcium on lipid and lipoprotein concentrations has been determined, the results of RCTs are contradictory. Recently, a systematic review concluded that calcium alone cannot be helpful to decrease blood concentrations of TC and TG, whereas, it might modulate concentrations of LDL-C and HDL-C.

Vitamin D can also be effective on serum concentrations of lipid and lipoprotein through direct and indirect mechanisms (Jorde and Grimnes, 2011). One of the main effects of vitamin D is the increase in calcium absorption from the intestine, which could affect the amount of fat absorption. As previously explained, elevated levels of calcium reduce hepatic TG formation and/or secretion (Boon et al., 2007). In addition, vitamin D can affect the blood level of lipids through the suppression of the PTH secretion (Zemel et al., 2000). Evidence suggests that increased levels of PTH are associated with high blood pressure, obesity and increased mortality (Jorde et al., 2005; Kamycheva et al., 2004). It has also been reported that increased PTH is associated with a reduction in lipolysis (Zemel et al., 2000). In addition, vitamin D can affect insulin secretion and insulin sensitivity, thereby indirectly affecting the metabolism of lipids (Kamycheva et al., 2007). As well as calcium, results of the RCTs assessed the effect of vitamin D on lipid profile, are inconsistent. A systematic review and meta-analysis indicated that vitamin D supplementation significantly reduced serum concentrations of LDL, TC and TG, and significantly increased serum levels of HDL (Mirhosseini et al., 2018).

Results of our meta-analysis indicated that co-supplementation of calcium and vitamin D significantly increased serum levels of HDL-C. According to the results of subgroup analysis, calcium and vitamin D co-supplementation was effective in increasing HDL-C levels in short-term supplementation (equal or less than 8 weeks). In addition, we found that LDL-C levels significantly reduced in equal or less than 8 weeks supplementation. Results of the previous meta-analysis indicated that vitamin D supplementation alone was effective in increasing HDL-C levels in short-term supplementation (Mirhosseini et al., 2018). Moreover, we found that lower doses of vitamin D and calcium

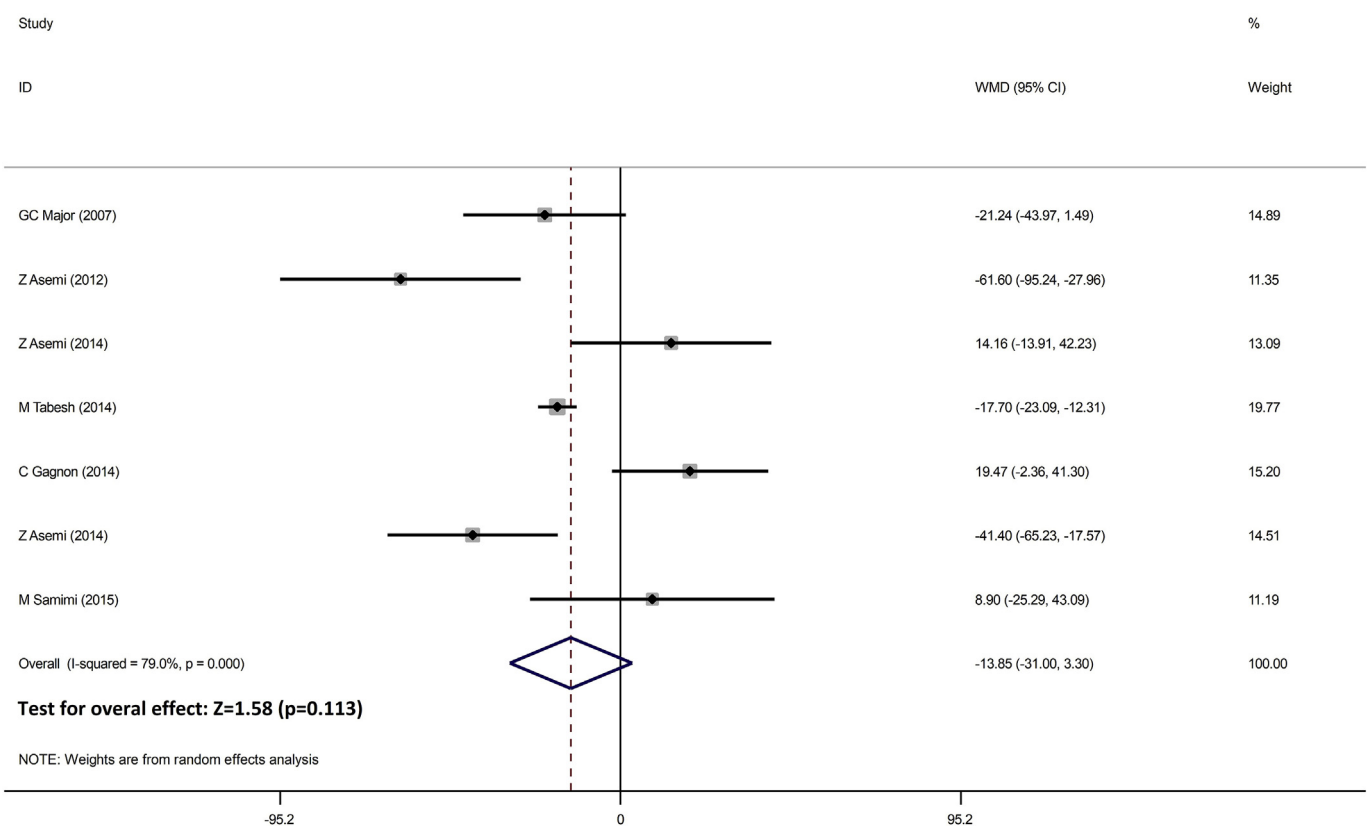

Fig. 2. Forest plot of the random-effects meta-analysis of the effect of combined vitamin D and calcium supplementation on triglyceride.

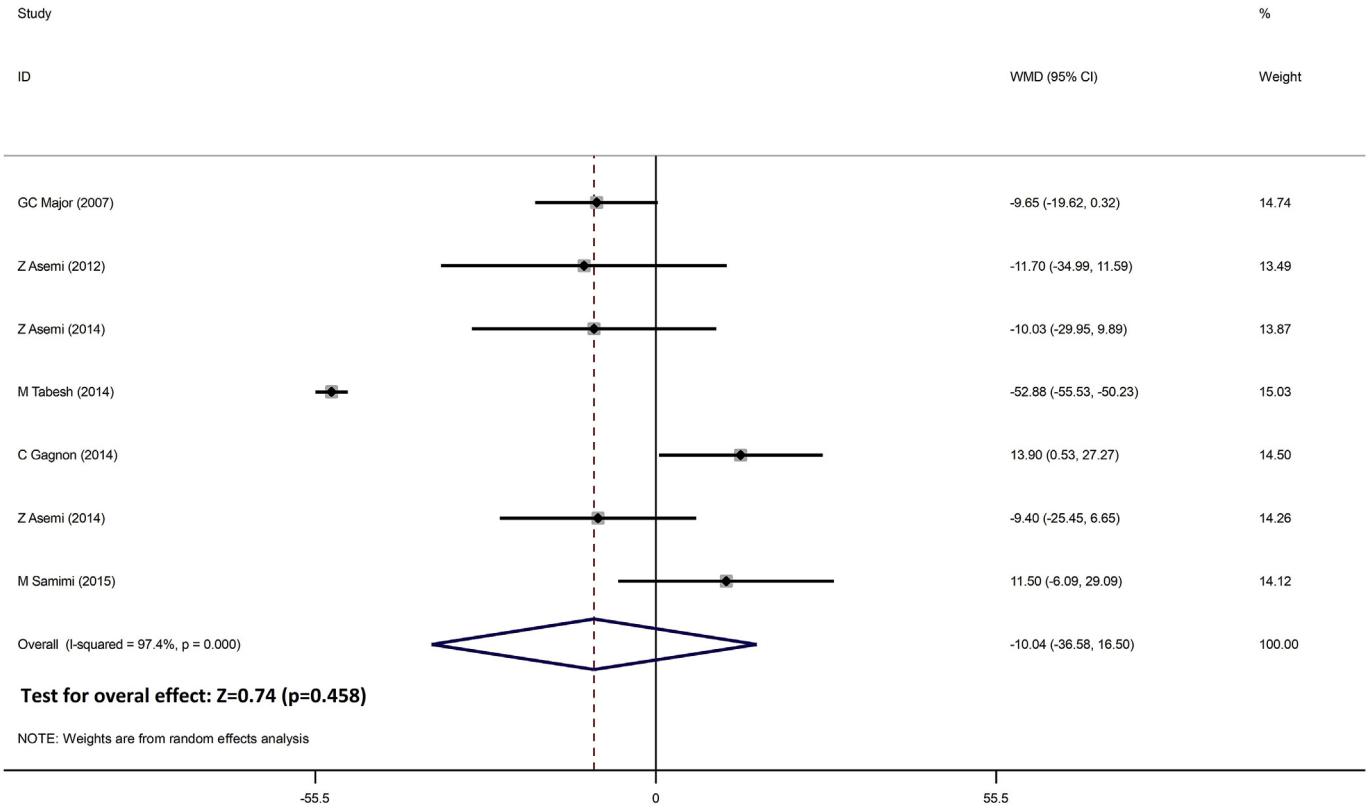

Fig. 3. Forest plot of the random-effects meta-analysis of the effect of combined vitamin D and calcium supplementation on total cholesterol.

Table 2
Subgroup analyses of calcium and vitamin D co-supplementation on lipid profile.

	No	WMD (95%CI)	*p* within group	*P* heterogeneity	I^2
Subgroup analyses of calcium-vitamin D co-supplementation on triglycerides level.					
Baseline serum triglycerides (mg/dl)					
< 150	3	−14.14 (−49.51, 21.21)	0.433	0.001	86.2%
> 150	4	−13.79 (−39.17, 11.58)	0.287	0.003	78.2%
Trial duration (week)					
> 8	4	−12.70 (−46.15, 20.75)	0.457	< 0.001	83.4%
≤8	3	−16.31 (−39.26, 6.62)	0.163	0.013	77.1%
Vitamin D (IU) and Calcium (mg) Dose					
≤400 IU/day and ≤600 mg	2	−39.43 (−78.79, −0.07)	**0.050**	0.051	73.7%
≥2000 IU/day and ≥1000 mg	5	−4.90 (−25.55, 15.75)	0.642	< 0.001	81.2%
Subgroup analyses of calcium-vitamin D co-supplementation on total cholesterol level.					
Baseline serum cholesterol (mg/dl)					
< 200	5	−13.94 (−44.66, 16.78)	0.374	< 0.001	97.9%
> 200	2	1.20 (−21.38, 23.79)	0.917	0.119	58.8%
Trial duration (week)					
> 8	4	1.37 (−12.66, 15.42)	0.847	0.016	71.0%
≤8	3	−24.97 (−59.63, 9.68)	0.158	< 0.001	95.5%
Vitamin D (IU) and Calcium (mg) Dose					
Low –dose (≤400 IU/day and ≤600 mg)	2	−9.96 (−19.13, −0.80)	**0.033**	0.874	0.0%
high –dose (≥2000 IU/day and ≥1000 mg)	5	−9.71 (−44.98, 25.55)	0.589	< 0.001	97.7%
Subgroup analyses of calcium-vitamin D co-supplementation on HDL-C level.					
Baseline serum HDL-C (mg/dl)					
> 50	3	3.74 (−0.86, 8.35)	0.112	0.065	63.4%
< 50	4	4.03 (−1.42, 9.49)	0.147	< 0.001	88.6%
Trial duration (week)					
> 8	4	2.32 (−1.99, 6.63)	0.292	0.012	72.4%
≤8	3	6.71 (3.18, 10.25)	< **0.001**	0.105	55.7%
Vitamin D (IU) and Calcium (mg) Dose					
Low –dose (≤400 IU/day and ≤600 mg)	2	1.62 (−3.46, 6.70)	0.532	0.192	41.3%
high –dose (≥2000 IU/day and ≥1000 mg)	5	4.85 (0.77, 8.93)	**0.020**	< 0.001	84.9%
Subgroup analyses of calcium-vitamin D co-supplementation on LDL-C level.					
Baseline serum LDL-C (mg/dl)					
> 100	5	−2.51 (−10.83, 5.81)	0.554	0.028	60.1%
< 100	1	−17.76 (−20.41, −15.10)	< **0.001**	–	–
Trial duration (week)					
> 8	4	0.85 (−9.15, 10.85)	0.867	0.043	63.2%
≤8	3	−14.49 (−23.32, −5.67)	**0.001**	0.121	52.7%
Vitamin D (IU) and Calcium (mg) Dose					
Low –dose (≤400 IU/day and ≤600 mg)	2	−7.30 (−15.03, 0.42)	0.064	0.309	3.4%
high –dose (≥2000 IU/day and ≥1000 mg)	5	−5.42 (−18.45, 7.59)	0.414	< 0.001	88.0%

Abbreviations: CI, confidence interval; HDL-C, High-density lipoprotein cholesterol; LDL-C, Low-density lipoprotein cholesterol; WMD, weighted mean differences.

significantly reduced TG and TC levels, whereas, higher doses could significantly increase HDL-C levels. Our results are in line with the recent systematic review and meta-analysis which indicated that lower doses of vitamin D supplementation alone was effective in reducing TC (Mirhosseini et al., 2018). However, our results regarding HDL-C were in contrast with the results of meta-analysis by Mirhosseini et al. which indicated that lower doses of vitamin D could increase the HDL-C levels (Mirhosseini et al., 2018). The discrepancy found between the results of our meta-analysis and previous meta-analysis could partly be due to the difference in subjects included to the meta-analysis and difference in the cut-points used for the subgroup analysis. In the meta-analyses by Mirhosseini et al., there was no restriction on the similarity of studies based on the types of participants, and included both healthy subjects and patients with different types of diseases (Mirhosseini et al., 2018). In addition, the cut-point which was used for the subgroup of vitamin D supplementation dose, in the meta-analysis of Mirhosseini et al., was 4000 IU/d, which was different from cut-point we used. Other variables such as baseline serum levels of 25(OH)D, baseline serum levels of lipoproteins, age, sex and weight of the participants can also influence the results. Therefore, further well designed studies with considering these covariates are needed.

Present systematic review and meta-analysis has several strengths. First, this is the first meta-analysis to assess the effect of calcium and vitamin D co-supplementation on lipids concentrations in overweight/obese subjects. Second, we included RCTs which examined complementary endpoints, providing a comprehensive review on this topic. Third, this review is based on an up to date literature search from a large number of databases. An important limitation of this meta-analysis is low number of trials which were available for the present meta-analysis that limits the strength of the conclusion; however, we hope this study will be helpful for future studies.

In conclusion, the present systematic review and meta-analysis indicated the beneficial effects of calcium and vitamin D co-supplementation on lipid profile of overweigh/obese subjects. We found that lower doses of vitamin D and calcium significantly reduced TG and TC levels. Furthermore, we found that the increasing effect of calcium and vitamin D co-supplementation on HDL-C was significant in equal or less than 8 weeks supplementation and in higher doses of vitamin D and calcium. In addition, we found that this co-supplementation significantly reduced LDL-C in equal or less than 8 weeks supplementation. However, further well-designed studies are needed to confirm the results of the present meta-analysis.

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Author contributions

AA and OA designed the study. OA and SK reviewed and selected the articles. SK and RC extracted needed data from articles. OA and AA

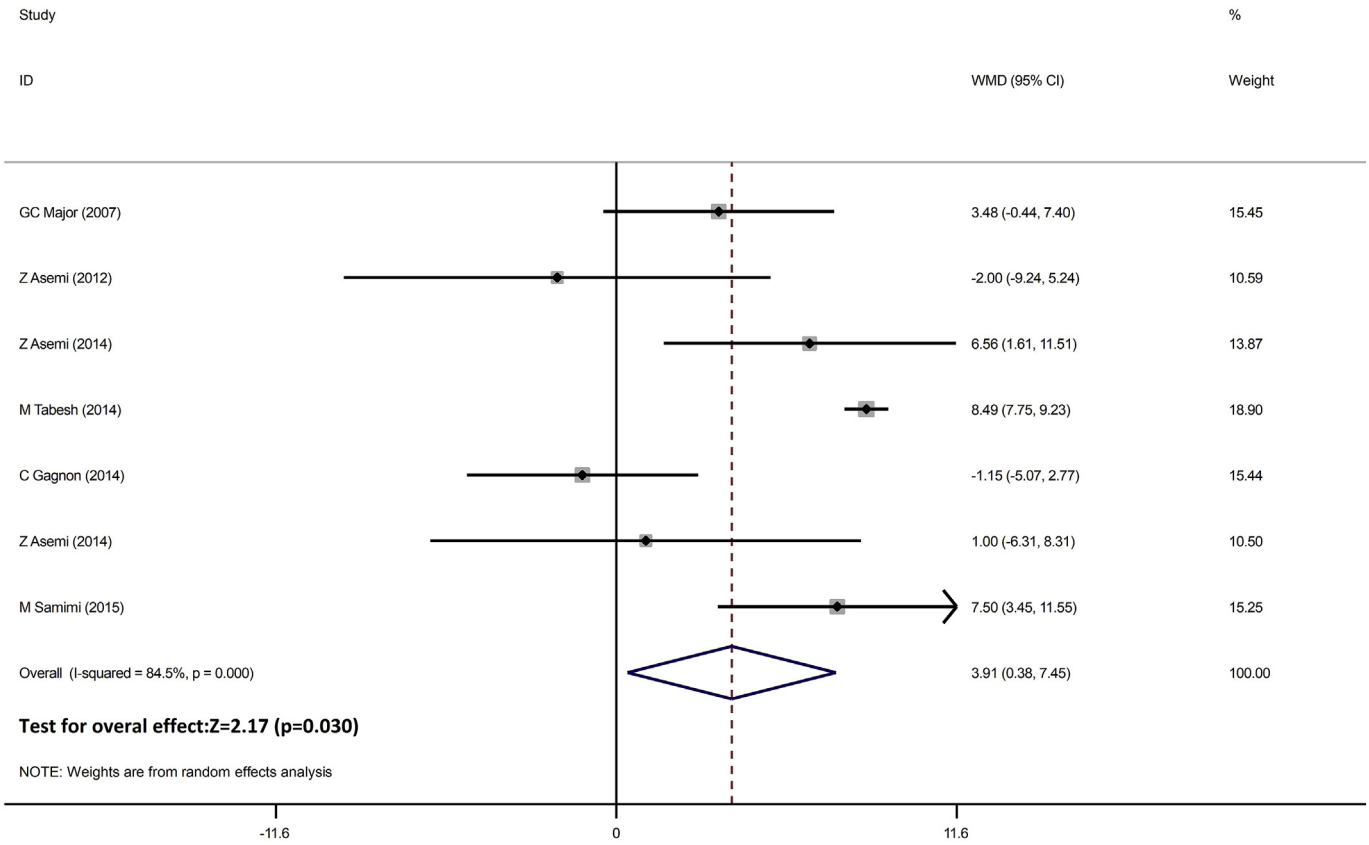

Fig. 4. Forest plot of the random-effects meta-analysis of the effect of combined vitamin D and calcium supplementation on high-density lipoprotein.

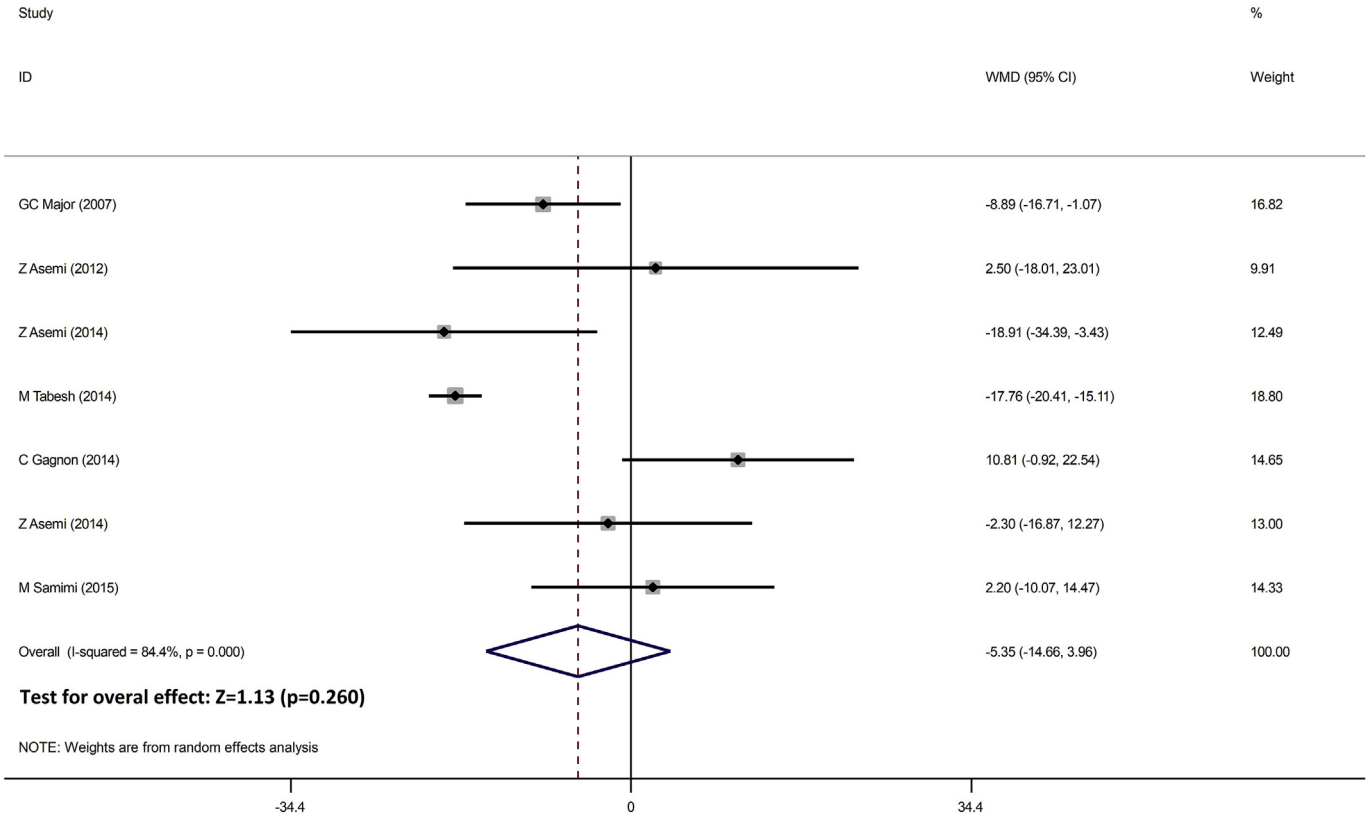

Fig. 5. Forest plot of the random-effects meta-analysis of the effect of combined vitamin D and calcium supplementation on low-density lipoprotein.

performed data analysis and interpretation. RC drafted the manuscript. AH revised the article for important intellectual content.

Declarations of interest

None.

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