Effect of Calcium-Vitamin D Co-Supplementation on Insulin, Insulin Sensitivity, and Glycemia: A Systematic Review and Meta-Analysis of Randomized Clinical Trials

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ABSTRACT

We conducted a systematic review and meta-analysis of randomized controlled trials (RCTs) to assess the effect of calcium-vitamin D co-supplementation on insulin, insulin sensitivity, and glycemia. A systematic search was carried out in Web of Science, PubMed, EMBASE, Scopus, and Cochrane library without any language and time restriction up to 12 August 2018, to retrieve the RCTs, which examined the effect of calcium and vitamin D co-supplementation on fasting blood glucose (FBG), insulin, HOMA-B, HOMA-IR, and QUICKI. Meta-analyses were carried out using a random effects model, and I2 indexes were used to evaluate the heterogeneity. Search yielded 2225 publications. Twelve RCTs with 4395 patients were eligible. Results demonstrated that calcium and vitamin D co-supplementation had significantly reducing effects on FBG, HOMA-IR and circulating levels of insulin. As the subgroup analysis demonstrated, short-term (≤ 12 weeks) calcium and vitamin D co-supplementation had a significant reducing effect on FBG. However, beneficial effects of calcium and vitamin D co-supplementation on circulating level of insulin and HOMA-IR were seen in both short-term and long-term (> 12 weeks) supplementations. Furthermore, we found that high doses of vitamin D and calcium co-supplementation (vitamin D ≥ 2000 mg/day and calcium ≥ 1000 mg/day) had significantly reducing effects on FBG, HOMA-IR and insulin. Present meta-analysis indicated the beneficial effects of high-dose and short-term combined vitamin D and calcium supplementation on insulin, insulin resistance and glycemia; however, further large-scale RCTs with adequate and multiple dosing schedules are needed.

Introduction

Insulin resistance is present in most patients with glucose intolerance or non-insulin-dependent diabetes mellitus (NIDDM), and in 25 % of normal-weight subjects with normal glucose tolerance [1]. In these situations, glucose intolerance can just be prevented when the β-cell is able to increase and maintain insulin secretion [1]. Failure to achieve this goal results in instability of glucose homeosta-sis, which is associated with many diseases [1]. An elevated blood level of glucose, insulin deficiency, and insulin resistance are the characteristic features of type 2 diabetes mellitus (DM) [2]. Type 2 DM has become a major problem for global health whose prevalence is expected to increase to 366 million by 2030 worldwide [3]. As one of the main causes of disability in 2015 [4], diabetes causes many social and economic problems and increases health costs

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worldwide [5]. Another complication associated with increasing insulin resistance and blood glucose levels is the cardiovascular disease, which requires intensive management of lipid and glucose concentration to reduce the complications [6]. The benefits of controlling serum levels of glucose in glucose related complications such as retinopathy, neuropathy and nephropathy have been reported in several randomized trials [7–9]. Although the treatment of these complications has improved over the past decades, the increasing prevalence of insulin resistance related complications highlight the importance of the innovative approaches for disease prevention and treatment.

There is a growing body of evidence suggesting that vitamin D status may influence several diseases, such as autoimmune disorders, cancer, diabetes, and cardiovascular disease [10]. The hypothesis of the possible association between diabetes and hypovitaminosis D was supported by detection of the nuclear receptor of vitamin D (VDR) in β-cells of the pancreas [11]. Polymorphism of VDR was associated with changes in insulin sensitivity and secretion, indicating vitamin D involvement in the pathogenesis of both types of diabetes [12, 13]. Since then, numerous randomized clinical trials (RCTs) have been conducted to confirm or reject the beneficial effects of vitamin D supplementation in patients with diabetes, however, the results were controversial [14, 15]. A systematic review and meta-analysis of the effect of vitamin D supplementation on glycemic control indicated that vitamin D supplementation had no significant effect on fasting blood glucose (FBG) [16].

Given the fact that vitamin D and calcium can affect synergistically the function of pancreatic β-cells and improve the glycemic control [17], numerous studies have assessed the effect of calcium and vitamin D co-supplementation on glycemic control. A study by Pittas et al. [18] indicated that calcium and vitamin D co-supplementation in healthy adults with impaired fasting glucose (IFG) could attenuate increases in insulin resistance and glycemia. Whereas, another study by De Boer et al. [19] reported that calcium and vitamin D co-supplementation had no significant effect on parameters of glucose metabolism. In 2007, a systematic review and meta-analysis found that the combined calcium and vitamin D supplementation may be effective in preventing type 2 diabetes, especially in subjects with glucose intolerance [18]. Of note, they searched only MEDLINE through January 2007 and found only one RCTs regarding the calcium and vitamin D co-supplementation. Due to the inconsistent results found in the literature, we carried out a systematic review and meta-analysis of RCTs to assess the effect of calcium and vitamin D co-supplementation on insulin, insulin sensitivity, and glycemia.

Materials and Methods

We performed this systematic review and meta-analysis according to the guidelines of the 2009 preferred reporting items for systematic reviews and meta-analysis (PRISMA) statement [20].

Search strategy

In order to find articles related to the effect of vitamin D and calcium co-supplementation on glycemic indices, online databases Web of Science, PubMed, EMBASE, Scopus, and Cochrane library were systematically searched without any language and time restriction up to 12 August 2018, with the following search keywords in titles, abstracts and keywords: "vitamin D or cholecalciferol or ergocalciferol or alphacalcidol or alfacalcidol or calcitriol or paricalcitol or doxercalciferol or vitamin D2 or vitamin D3" and" diabetic or diabetes mellitus or glucose tolerance or insulin resistance or type 2 diabetes or FBG fasting blood glucose or HbA1c or hemoglobin A1c or HOMA-IR or homeostatic model assessment or Insulin or T2DM or fasting blood sugar or FBS" and "Intervention or controlled trial or randomized or random or randomly or placebo or assignment or clinical trial or Trial". We also used parentheses, asterisks and quotation marks to search for the exact terms and Boolean operators (AND and OR) for designing our search strategy. Moreover, a manual search and reference lists check of all included studies, and related reviews were performed to identify further relevant articles. Initially, 2225 studies were identified, of which finally 13 unique studies meeting inclusion criteria were selected for inclusion in this meta-analysis. The process of study selection is shown in the flow diagram (▶ **Fig. 1**). Reference management was carried out using EndNote X7.5. (Supplementary **File 1**, search strategy).

Study selection

Articles were eligible for inclusion in this meta-analysis if they fulfilled the following criteria:

1) RCTs of oral calcium and vitamin D co-supplementation; 2) trials with duration of more than one week; and 3) reported mean or median values in baseline and at the end of supplementation in intervention and control groups with SD, SEM or 95 % CI. The exclusion criteria were as follows: 1) studies with no placebo group; 2) case-control, cross-sectional, cohort design and review studies; 3) studies which used a combination of other vitamins and minerals, including vitamin D and Calcium; 4) studies conducted in animal models; and 5) studies that were not available.

Data extraction

After removing duplicates, titles and abstracts of all studies were assessed independently by two reviewers (S.K. and M.Z.) to find potentially relevant studies for reading the full text. Finally, full text of each article was reviewed to determine whether the article is qualified for inclusion. Any disagreement about study inclusion was consulted with a third author (O.A.). Major demographic and clinical data of each included trial containing the following items of first author's name, publication year, and origin of country, study design, dosage and duration of Calcium and vitamin D co-supplementation and sample size in intervention and control groups were extracted. Demographic data included sex, mean age and body mass index (BMI), baseline and final values of metabolic variables (FBG, Insulin, HOMA-B, HOMA-IR, QUICKI) in control and treatment groups.

Quality assessment

Quality of each included study was assessed using 5-point scale Jadad score [21]. This scale assesses the quality of RCTs and includes random allocation (up to 2 points), double blinding (up to 2 points), and description of withdrawals and dropouts (up to 1 point). Studies with the scores of 3 and higher are generally considered as a high quality study.
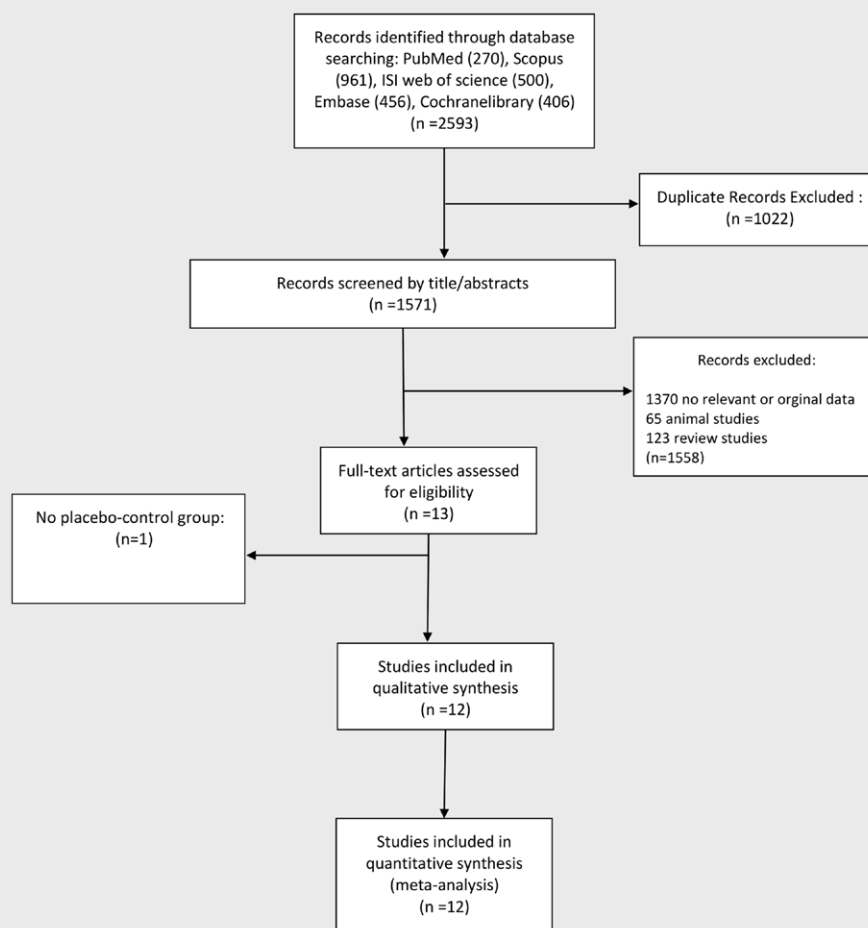
▶ **Fig. 1** Flowchart of study selection for inclusion trials in the systematic review.

Data synthesis and statistical analysis

Mean and standard deviation (SD) of related variables at baseline and post intervention was used to compare changes between control and intervention groups. When S.D of change was not reported, it was calculated using following formula: s.d. = square root [(s.d. pre-intervention)^2 + (s.d. post-intervention)^2 − (2 R × s.d. pre-intervention × s.d. post-intervention)]. A correlation coefficient of 0.8 was assumed as R-value of the above-mentioned formula. Reported SE in some studies was converted to SD by multiplying SE with √n, where n is the sample size of each group. If the variables were reported in median and range (or 95% confidence interval), mean and SD were estimated according to the method by Hozo et al., [22]. When the variables reported in the graphic form, the software GetData Graph Digitizer 2.24 [23] was used to digitize and extract the data. Random effects model was used to calculate pooled effect size of outcome data. We performed subgroup analysis based on pre-specific characteristics, including gender, health status, age, dose, study quality, study duration, and baseline levels of clinical parameters (HOMA-IR, FBG and Insulin) to detect possible sources of heterogeneity. Publication bias was assessed using visual assessment of funnel plots, Beg-test and Egger's regression asymmetry test. We performed the sensitivity analysis by conduct-

ing one-study remove (leave-one-out) approach, to estimate the impact of each trial on the pooled effect size. Between-study heterogeneity was examined using Q test and I-square (I^2) test [24]. All analyses were conducted using STATA v.12 (Stata Corporation, College Station, TX, USA).

Results

Study selection

In our initial search, a total of 2593 publications were found. Of these, 1022 duplicate articles were excluded initially, and remaining articles were assessed carefully by title and abstract. Upon screening the titles and abstracts, 13 full-text articles were retrieved and assessed for eligibility. Finally, 12 unique studies meeting inclusion and exclusion criteria were included in this meta-analysis. The process of study selection is shown in the flow diagram (▶ **Fig. 1**).

Study characteristics

All 12 studies [18, 19, 25–34] were double-blinded and placebo-controlled studies. The intervention durations were from 6 to 312 weeks.

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Data are pooled from 12 studies with 4395 participants in the intervention arm and 4551 participants in the control arm. Age range of the participants was 18 to 71.7 years old. Seven studies were conducted in Iran [27–32, 34], 1 in Canada [25], and 4 in USA [18, 19, 26, 33]. All the included studies were parallel in design. Four studies were conducted on both genders [18, 26, 29, 33], and other studies enrolled females [19, 25, 27, 28, 30–32]. Basis on the jaded scale, 11 of the studies had good quality (≥3) [18, 19, 25, 26, 28–34] and quality score of one study was lower than 3 [27]. The supplementation doses also varied between studies. Supplementation dose of calcium was ranged from 500 mg/day to 1000 mg/day, and for vitamin D ranged from 200 IU/day to 50000 IU/week. The supplementation was calcium citrate in one study [18], and in other studies, it was calcium carbonate [19, 25–34]. Some studies were conducted on healthy subjects [18, 19, 25–27, 32] and other studies were conducted on patients [28–31, 33, 34]. Characteristics of the included studies are summarized in ▶ **Table 1**.

Publication bias

Based on Egger's test, there was no statistical evidence of publication bias among the included studies in the overall analysis, except for effects of vitamin D and calcium co-supplementation on QUICKI (p = 0.028). (Supplementary **File 1**)

Sensitivity analyses

To evaluate the strength of our results, we made a sensitivity analysis. However, removing each individual study by sensitivity analysis did not change the pooled effect size of FBG, insulin, HOMA-B, HOMA-IR, and QUICKI.

Meta-analysis

The forest plots of the effects of vitamin D and calcium co-supplementation on glycemic status are shown in ▶ **Fig. 2** and supplementary (▶ **Fig. 1S–4S**). In this systematic review and meta-analysis, we pooled and analyzed data from 10 studies evaluating the effects of vitamin D and calcium co-supplementation on FBG, 6 studies on insulin, 5 studies on HOMA-B, 7 studies on HOMA-IR and 5 studies on QUICKI. Results indicated that vitamin D and calcium co-supplementation had significantly reducing effects on FBG (pooled WMD = −2.28 (95 % CI: −3.76 to −0.80), p = 0.000, I^2 = 74.3 %), insulin (pooled WMD = −0.85 (95 % CI: −1.60 to −0.09), p = 0.000, I^2 = 72.8 %), and also on HOMA-IR (pooled WMD = −0.37 (95 % CI: −0.60 to −0.14), p = 0.000, I^2 = 85.5 %). However, vitamin D and calcium co-supplementation had no significant effect on HOMA-B (pooled WMD = −9.36 (95 % CI: −29.23 to 10.51, p = 0.000, I^2 = 91.8 %) and QUICKI (pooled WMD = 0.01 (95 % CI: −0.02 to 0.04), p = 0.000, I^2 = 97.1 %).

Subgroup analyses

Effect of combined vitamin D and calcium supplementation on FBG

Results of subgroup analyses (▶ **Table 1S**) indicated that heterogeneity disappeared in subgroups of subjects with baseline serum FBG > 100 mg/dl, calcium < 1000 mg/day or vitamin D < 2000 IU/day, participant's age ≥ 50, and in healthy subjects. Co-supplementation of vitamin D and calcium had significantly reducing effects on FBG in subgroups of subjects with baseline serum FBG < 100 mg/dl, Trial's

duration ≤ 12 weeks, calcium doses ≥ 1000 mg/day with vitamin D doses ≥ 2000 IU/day, female participants, participant's age < 50, and in high-quality studies with jadad score equal to 5.

Effect of combined vitamin D and calcium supplementation on insulin

Results demonstrated that heterogeneity disappeared in subgroups of subjects with baseline serum insulin < 10 mg/dl, Trial's duration > 12 week, calcium < 1000 mg/day or vitamin D < 2000 IU/day, studies included both sexes, participant's age ≥ 50, and in studies with the jaded score equal to 5. Reducing effect of vitamin D and calcium co-supplementation on HOMA-IR was seen in all the subgroups except in subgroups of calcium doses < 1000 mg/day or vitamin D doses < 2000 IU/day, participant's age ≥ 50, studies with the jadad scores lower than 5 and in healthy subjects (▶ **Table 2S**).

Effect of combined vitamin D and calcium supplementation on HOMA-IR

Subgroup analyses indicated that heterogeneity disappeared in subgroups of subjects with baseline HOMA-IR < 1.4, Trial's duration > 12 weeks, calcium < 1000 mg/day or vitamin D < 2000 IU/day, and high-quality studies with the jaded score equal to 5 (▶ **Table 3S**). Reducing effect of vitamin D and calcium co-supplementation on HOMA-IR was seen in all the subgroups except in subgroups of calcium doses < 1000 mg/day or vitamin D doses < 2000 IU/day, participant's age ≥ 50 and in healthy subjects.

Discussion

Results of the present meta-analysis demonstrated that calcium and vitamin D co-supplementation had significantly reducing effects on FBG, HOMA-IR, and circulating levels of insulin, whereas, this co-supplementation had no significant effects on HOMA-B and QUICKI. As the subgroup analysis demonstrated, short-term (≤ 12 weeks) calcium and vitamin D co-supplementation had a significant reducing effect on FBG. However, beneficial effect of calcium and vitamin D co-supplementation on circulating level of insulin and HOMA-IR were seen in both short-term and long-term (> 12 weeks) supplementation. Furthermore, we found that high doses of vitamin D and calcium co-supplementation (vitamin D ≥ 2000 mg/day and calcium ≥ 1000 mg/day) had significantly reducing effects on FBG, HOMA-IR, and insulin.

Several lines of evidence suggested the role of vitamin D in the function of pancreatic β-cells. Vitamin D seems to be able to improve insulin response to glucose [17]. Vitamin D may directly affect the function of β-cells through binding to the vitamin D receptors in β-cells [35]. Recently, it has been shown that the enzyme activating vitamin D, 1-α-hydroxylase, is also expressed in β-cells [35]. Although, the beneficial effects of vitamin D on the function of pancreatic β-cells are well documented, the results of the previous clinical trials regarding the effects of the vitamin D supplementation on glycemic control were inconsistent. A recent systematic review revealed that vitamin D supplementation had no significant effect on FBG [16]. Moreover, a systematic review and meta-analysis found that there was no sufficient evidence for the effectiveness of vitamin D supplementation as a method to improve insulin resistance and normal FBG in type 2 diabetes patients [36]. A re-

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Table 1 Characteristics of the included studies 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 [25]	2007	Canada	R/DB/PL	Overweight or obese	F	43.6/41.6	31.4/32.3	15	600	calcium carbonate	200	vitamin D3	30/33	4
AG Pittas (A) [40]	2007	USA	R/DB/PL	Normal fasting glucose (NFG)	F/M	70.6/71.7	26.1/26.2	156	500	calcium citrate	700	vitamin D3	108/114	4
AG Pittas (B) [40]	2007	USA	R/DB/PL	Impaired fasting glucose (IFG)	F/M	71.1/71.3	27.8/28.1	156	500	calcium citrate	700	vitamin D3	45/47	4
IH De Boer (A) [19]	2008	USA	R/DB/PL	Women's Health	F	NR/NR	NR/NR	156	1,000	calcium carbonate	400	vitamin D3	866/890	4
IH De Boer (B) [19]	2008	USA	R/DB/PL	Women's Health	F	NR/NR	NR/NR	312	1,000	calcium carbonate	400	vitamin D3	738/771	4
IH De Boer (C) [19]	2008	USA	R/DB/PL	Women's Health	F	NR/NR	NR/NR	156	1,000	calcium carbonate	400	vitamin D3	795/818	4
IH De Boer (D) [19]	2008	USA	R/DB/PL	Women's Health	F	NR/NR	NR/NR	312	1,000	calcium carbonate	400	vitamin D3	718/739	4
IH De Boer (E) [19]	2008	USA	R/DB/PL	Women's Health	F	NR/NR	NR/NR	156	1,000	calcium carbonate	400	vitamin D3	197/211	4
IH De Boer (F) [19]	2008	USA	R/DB/PL	Women's Health	F	NR/NR	NR/NR	312	1,000	calcium carbonate	400	vitamin D3	172/178	4
IH De Boer (G) [19]	2008	USA	R/DB/PL	Women's Health	F	NR/NR	NR/NR	156	1,000	calcium carbonate	400	vitamin D3	189/195	4
IH De Boer (H) [19]	2008	USA	R/DB/PL	Women's Health	F	NR/NR	NR/NR	312	1,000	calcium carbonate	400	vitamin D3	171/173	4
J Mitri [26]	2011	USA	R/DB/PL	High risk of diabetes	F/M	57/59	33/32	16	400	calcium carbonate	2000	vitamin D3	23/24	5
Z Asemi [27]	2012	IRAN	R/SB/PL	Pregnant	F	NR/NR	28.5/26.7	9	500	calcium carbonate	200	vitamin D3	24/25	2
Z Asemi [28]	2014	IRAN	R/DB/PL	GDM	F	28/30	29/30.5	6	1,000	calcium carbonate	2380	vitamin D3	28/28	5
M Tabesh [29]	2014	IRAN	R/DB/PL	Type 2 diabetes	F/M	49.8/51	29.9.30.3	8	1,000	calcium carbonate	7142	vitamin D3	30/30	4
Z Asemi [30]	2014	IRAN	R/DB/PL	Polycystic ovary syndrome	F	24.9/24.3	27.3/27.5	8	1,000	calcium carbonate	7142	vitamin D3	26/26	5
F Foroozanfard [31]	2015	IRAN	R/DB/PL	Polycystic ovary syndrome	F	NR/NR	NR/NR	8	1,000	calcium carbonate	7142	vitamin D3	26/26	4
M Samimi [33]	2015	IRAN	R/DB/PL	Pregnant	F	27.3/27.1	27.4/25.6	12	1,000	calcium carbonate	3571	vitamin D3	30/30	4
J Muhamma (A) [34]	2018	USA	R/DB/PL	HIV-infected adults	F/M	36/31	25/24	24	1,000	calcium carbonate	4000	vitamin D3	79/86	3
J Muhamma (B) [34]	2018	USA	R/DB/PL	HIV-infected adults	F/M	36/31	25/24	48	1,000	calcium carbonate	4000	vitamin D3	79/86	3
Z Asemi [32]	2018	IRAN	R/DB/PL	Pregnant	F	25/24	27.9/27	9	500	calcium carbonate	200	vitamin D3	21/21	5

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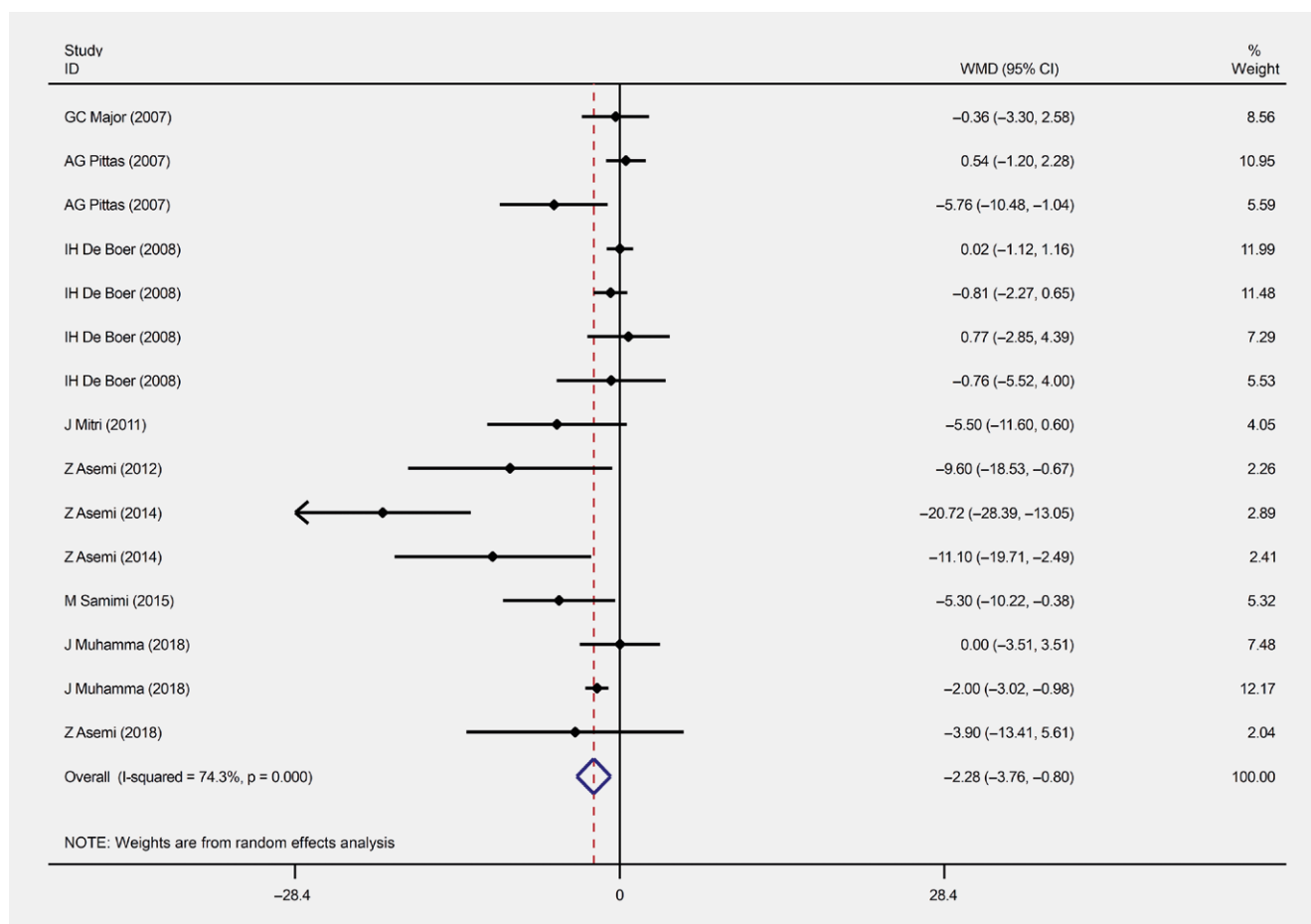
▶ **Fig. 2** Forest plot of the random-effects meta-analysis of the effect of combined vitamin D and calcium supplementation on fasting blood glucose (FBG).

cent meta-analysis found that vitamin D supplementation had no significant reducing effect on FBG, however, subgroup analysis indicated that vitamin D supplementation could improve glycemic control in vitamin D deficient type 2 DM patients [37].

Indirect effects of vitamin D on the function of pancreatic β-cell may be mediated through its role in regulating calcium flux through the pancreatic β-cell [38]. The process of insulin secretion is highly dependent to calcium, thus, any changes in calcium flux can adversely affect the secretory function of β-cell [17]. In addition, a very narrow range of intracellular calcium is needed for insulin-dependent intracellular processes, therefore, any change of calcium levels in insulin-responsive tissues such as adipose tissue and skeletal muscles results in peripheral insulin resistance [38]. Although, basic and animal studies [38, 39] suggested that calcium and vitamin D could synergistically improve the function of β-cells and glycemic control, results of the RCTs assessed the effect of vitamin D and calcium co-supplementation on insulin secretion and glycemic control were inconsistence. In 2007, a systematic review and meta-analysis reported that vitamin D alone had no effect in healthy individuals, but vitamin D and calcium co-supplementation may be beneficial in optimizing glucose metabolism in populations at risk for type 2 DM [17]. It should be noted that this systematic review and meta-analysis searched only MEDLINE for English-lan-

guage literature through January 2007, and found only one study regarding vitamin D and calcium co-supplementation. Results of the present systematic review and meta-analysis indicated that calcium and vitamin D co-supplementation significantly reduced FBG, HOMA-IR, and insulin levels.

As subgroup analyses indicated, the beneficial effects of vitamin D and calcium co-supplementation were seen in the subgroup of subjects with FBG levels lower than 100 mg/dl, and not in subjects with FBG levels ≥ 100 mg/dl. The possible reason that can be assumed for these results is that all the studies in the subgroup of FBG ≥ 100 mg/dl [19, 25, 40] administered lower doses of vitamin D and calcium (vitamin D ≤ 700 IU/day and calcium ≤ 1000 mg/day). In addition we found that co-supplementation of higher doses of calcium and vitamin D, (calcium ≥ 1000 mg/day and vitamin D ≥ 2000 IU/day) had reducing effects on FBG, circulating levels of insulin and HOMA-IR. A growing body of evidence suggests that vitamin D and calcium intakes higher than the current recommendations may lead to better health outcomes [17, 41]. Results of the Nurses' Health Study indicated that a combined intake of > 1200 mg calcium and > 800 IU vitamin D was associated with a lower risk of type 2 DM as compared with lower doses [42]. Optimal blood concentrations of 25(OH)D is critical for the positive effects of vitamin D on glycemic control. Optimal blood concentrations of 25(OH)D for patients with DM has not been specified, but

the most advantageous blood levels of 25(OH)D seems to be above 40 ng/ml [17]. Approximately 1000 IU/d of vitamin D are essential to achieve such a concentration [16]. In 2017, a systematic review and meta-analysis reported that the dose of vitamin D supplementation ≥ 1000 IU/day had a reducing effect on FBG levels [37]. Recently, a systematic review and meta-analysis indicated that daily doses of vitamin D ≥ 2000 IU/day had a positive impact on glycemic control [43]. In relation to calcium, it is difficult to determine the insufficiency of calcium status by biochemical methods, but suboptimal intake of calcium has been reported in different populations [44, 45]. Evidence suggests that daily intake of calcium more than 1200 mg may be desirable for patients with DM [17].

In addition, the present meta-analysis indicated that short-term (≤ 12 weeks) co-supplementation of calcium and vitamin D had a significant reducing effect on FBG. It should be noted that most short-term studies have used high doses of vitamin D and calcium for supplementation. Given the fact that achieving optimal circulating levels of 25(OH)D is critical for positive effects of vitamin D on glycemic control, thus, as described above, daily intake of high-dose vitamin D is important to achieve this goal. Previous systematic review and meta-analysis studies, which examined the effect of vitamin D alone on glycemic control, have also reported that short-term supplementation of vitamin D was beneficial in optimizing glucose metabolism. In 2015, a systematic review reported that short-term supplementation of vitamin D supplementation had a beneficial effect on glycemic control [16]. Furthermore, a recent systematic review and meta-analysis indicated that high-dose and short-term supplementation of vitamin D alone had beneficial effects on insulin resistance and FBG [43]. However, in 2017, a systematic review and meta-analysis reported that neither short-term and nor long-term vitamin D supplementation has significant effect on FBG [46].

The present systematic review and meta-analysis have several strengths. We included RCTs which examined complementary endpoints, providing a comprehensive review on this topic. This review is based on an up to date literature search from a large number of databases and included 12 studies with 4395 participants in the intervention arm and 4551 participants in the control arm. Present study has also several limitations. First, we did not limit the systematic search to a particular disease, which led to an increase in heterogeneity. However, by subgroup analysis, heterogeneity decreased in some of the subgroups. Second, although we conducted a comprehensive search of the electronic literature, there might be studies that have not been included. Finally, the small sample size of the individual studies limits the strength of the conclusion of the present meta-analysis, however, we hope this study will be helpful for future studies.

Conclusions

In conclusion, present meta-analysis indicated that calcium and vitamin D co-supplementation had reducing effects on FBG, HOMA-IR and circulating levels of insulin. However, the beneficial effects of combined vitamin D and calcium supplementation were seen in higher doses of both calcium and vitamin D. Furthermore, present meta-analysis indicated that short-term co-supplementation of calcium and vitamin D can be effective in reducing FBS. How-

ever, we found that both short-term and long-term co-supplementations has reducing effects on both HOMA-IR and circulating insulin. Further large-scale RCTs with adequate and multiple dosing schedules of calcium and vitamin D co-supplementation are needed to fully determine the role of calcium and vitamin D co-supplementation in optimizing glucose metabolism, especially in patients with diabetes.

Author Contributions

AA and OA designed the study. SK and MZK reviewed and selected the articles. OA and SK extracted needed data from articles. AA and OA performed data analysis and interpretation. AA drafted the manuscript.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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