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The effects of vitamin D supplementation on indices of glycemic control in Iranian diabetics: A systematic review and meta-analysis

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ABSTRACT

Background and purpose: This systematic review and meta-analysis aimed to assess the effects of vitamin D supplements on indices of glycemic control [homeostatic model assessment-insulin resistance (HOMA-IR), hemoglobin A1C (HbA1C), fasting blood glucose (FBG), and quantitative insulin-sensitivity check index (QUICKI) and lipid profile in diabetic patients.

Methods: Eight databases were searched, for randomized controlled trials (RCTs) or cross-sectional and cohort studies that have been published up to December 2017. We used the comprehensive meta-analysis (CMA) software for all statistical analysis and used the I^2 index for assessing heterogeneity. A p value of < 0.05 was considered as statistically significant.

Results: We found 621 articles, and after the exclusion of ineligible publications, 82 studies remained to be assessed of which 37 were used for meta-analysis. Vitamin D supplementation was associated with a significant improvement in FBG (p = 0.001 and 95% CI: −0.526 to −0.136) and HbA1C (p = 0.003 and 95% CI: 1.719 to −0.361) in individuals with type 2 diabetes mellitus (T2DM); while in women with gestational diabetes mellitus (GDM) the reduction in FBG (p = 0.071 and 95% CI: −0.873 to −0.035) and HbA1C (p = 0.199 and 95% CI: 3.270 to 0.681) failed to reach statistical significance. Treatment with vitamin D supplements was associated with an improvement in HOMA-IR in pregnant diabetic women (p = 0.028 and 95% CI: 0.924 to −0.053) and for individuals with diabetes mellitus (p = 0.005 and 95% CI: 1.772 to −0.319). The pooled result of the cross-sectional meta-analysis indicated that serum vitamin D concentrations were significantly lower in diabetic patients than in healthy controls (p = 0.018 and 95% CI: 0.587 to −0.054).

Conclusion: This meta-analysis suggests that vitamin D supplementation improves indices of glycemic control (FBG, HOMA-IR, and HbA1C) in patients with diabetes mellitus. Hence, vitamin D supplements may be of potential therapeutic value in diabetic patients, as an adjuvant therapy along with other treatments.

1. Introduction

Diabetes mellitus, is one of the most common chronic metabolic disorders and a significant global health concern [1]. Diabetes is characterized by hyperglycemia caused by insufficient secretion of insulin, insulin resistance, or both [2]. Deleterious long-term effects of

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diabetes include macro- and micro-vascular disease, neuropathy, and nephropathy [3]. Furthermore, there is a relationship between diabetes and an increased risk of some cancers, that include: pancreatic, breast and colorectal cancers [4,5]. The International Diabetes Federation (IDF) has estimated that the number of people with diabetes is 425 million globally, of whom two-thirds live in industrial areas [6]. More than 60% of diabetic patients globally are located in Asia [7]. Approximately 4.5 million adult diabetic patients live in Iran and it is estimated 9.2 million people will be diabetic by 2030 [8]. There are three main categories of diabetes mellitus [2]:

- Type 1 diabetes mellitus (T1DM): T1DM or Insulin dependent diabetes mellitus (IDDM) is an autoimmune disease, in which pancreatic beta cells are targeted for destruction by T-cells [9], and in which genetic and environmental factors have an important role [10].
- Type2 diabetes mellitus (T2DM): T2DM is known as "non-insulin-dependent- diabetes mellitus" (NIDDM). This is the most common form of diabetes mellitus, and is associated with insulin resistance [11].
- Gestational diabetes mellitus (GDM): GDM is glucose intolerance, often associated with hyperlipidemia and insulin resistance [12,13] that arises in the second or third trimester of pregnancy, and can affect women without a past history of impaired glucose tolerance, and has a negative impact on fetal and neonatal well-being [11,14].

Vitamin D is a pro-hormone [15] that has an important role in insulin secretion [16], although its classical role is in the regulation of intestinal absorption of calcium, phosphate and their homeostasis [17]. Its sources include dermal synthesis following exposure to sunlight, from the diet (salmon, mackerel) and dietary fortification and supplements [18,19]. Vitamin D deficiency and insufficiency is now becoming a global health concern and affects over one billion children and adults [20,21]. Some studies have shown a high prevalence of vitamin D deficiency in tropical and sub-tropical countries that include: Iran, Turkey, China, India and, Saudi Arabia [22]. In Iran, approximately (3.9–6.6 million) people are affected with DM [6]. Vitamin D deficiency is associated with hypertension [23], cardiovascular disease [24], glucose intolerance, insulin resistance and increased risk of diabetes [25]. A serum 25-hydroxyvitamin D [25(OH)D] level of < 20 ng/ml is associated with increased risk of colon, prostate, and breast cancer [26,27]. There appears to be an inverse relationship between the risk of DM, its complications and, serum 25(OH) D levels [28,29]. Therefore, DM is more common in vitamin D deficient subjects and vitamin D may also have beneficial anti-inflammatory effects [31]. There have been trials of vitamin D supplementation in individuals with DM [30,31] although there has been no comprehensive evaluation of the association between vitamin D and DM. Therefore, we aimed to conduct this systematic and meta-analysis by pooling the results from clinical trials and cross-sectional studies to investigate the potential relationship between vitamin D and DM.

2. Method

2.1. Search of literature

Relevant articles were identified using PubMed, Scopus, Web of Science, Cochrane Library, Google Scholar, ScienceDirect, Scientific Information Database (SID) and IranMedex up to December 2017. The search terms used were the following combination of keywords: ("vitamin D" or Vit D "25(OH)D") AND (diabetes or DM or diabetic) AND Iran) [MeSH Terms] OR ("vitamin D" or "25(OH)D") AND (diabetes or DM or diabetic) AND Iran) [All Fields], and Persian keywords in the title, abstract, and keywords. Initially, we evaluated all original articles in both English and Persian language including cross-sectional studies, cohort and randomized controlled trials that assessed the correlation and effect of vitamin D with or on DM, with no limitation for date. In the case of RCTs, we included all clinical trials with vitamin D (in forms of supplement or enriched in food) as the intervention and calcium, or placebo, as a control. The outcomes of interest in these studies were: fasting blood glucose (FBG), HbA1C and homeostatic model assessment-insulin resistance (HOMA-IR). Cell-line, animal experiments, review articles, laboratory studies, irrelevant topics, duplicate publication, non-clinical trials, and case reports were excluded. Other exclusion criteria included: incomplete data sets, the difference in baseline characteristics of all outcomes of interest, or lacking data about their similarity at baseline (in RCTs), book chapters, an absence of relevant data, lack of accurate data needed for our analysis. The quality appraisal for each article was performed according to particular criteria outlined by Joanna Briggs for cross-sectional studies and RCTs [32]. Studies with high scores ($> 50\%$) were considered to be high quality.

2.2. Data extraction

Data extracted included: the last name of the first author and publication year, location and type of study, sample size with the drop-out rate of population if available, population characteristics (number, age, sex), serum vitamin D concentration, dose, and duration of intervention 25(OH)D, assessment of further outcomes and limitation of the study were noted. In some studies, for which relevant data were missing, contact was made with the principal authors for more information. All the articles included were independently assessed by two reviewers (MR and RS) who read the full-text of the papers, and a consensus was reached in case of any inconsistency with the involvement of a third author (M. E).

2.3. Statistical analysis

Comprehensive meta-analysis (CMA) software was used for all statistical analysis. The I^2 index was used to assess heterogeneity, and in case of heterogeneity (I^2 value $> 50\%$). A $P < 0.05$ was considered statistically significant.

2.4. Search results and study characteristics

Fig. 1 shows the study selection data. We identified 621 articles using a systematic search, of which 53 studies were excluded because of duplication. From the remaining 568 studies, 463 publications were excluded because they were review articles, laboratory studies, irrelevant topics, duplicate publication, or non-clinical studies. The remaining 105 papers were evaluated for eligibility by examining their full text and 23 studies excluded because of incomplete data, or because they were book chapters, or animal studies. Finally, 82 articles remained to be assessed. There were 52 RCTs, 29 cross-sectional and one cohort study. These 82 studies were analyzed based on the quality measurement scale and inclusion and exclusion criteria. Although 82 studies were found to be appropriate for systematic analysis, 45 studies were excluded because the groups were not matched and differed significantly for glycemic indices at baseline. Some studies investigated gene polymorphisms, and did not document glycemic indices. A total of 37 articles were used for meta-analysis. In all, 11614 and 1673 individuals were included in the systematic review and meta-analysis, respectively.

2.4.1. The relation between serum vitamin D and measures of diabetes mellitus

Table 1 shows the results of RCTs on the effects of vitamin D supplementation or vitamin D fortified food versus placebo, calcium or non-fortified food. The data indicate that vitamin D supplementation significantly reduced HOMA-IR, HbA1C, fasting blood glucose (FBG), and high-sensitivity C-Reactive Protein (hs-CRP). Vitamin D

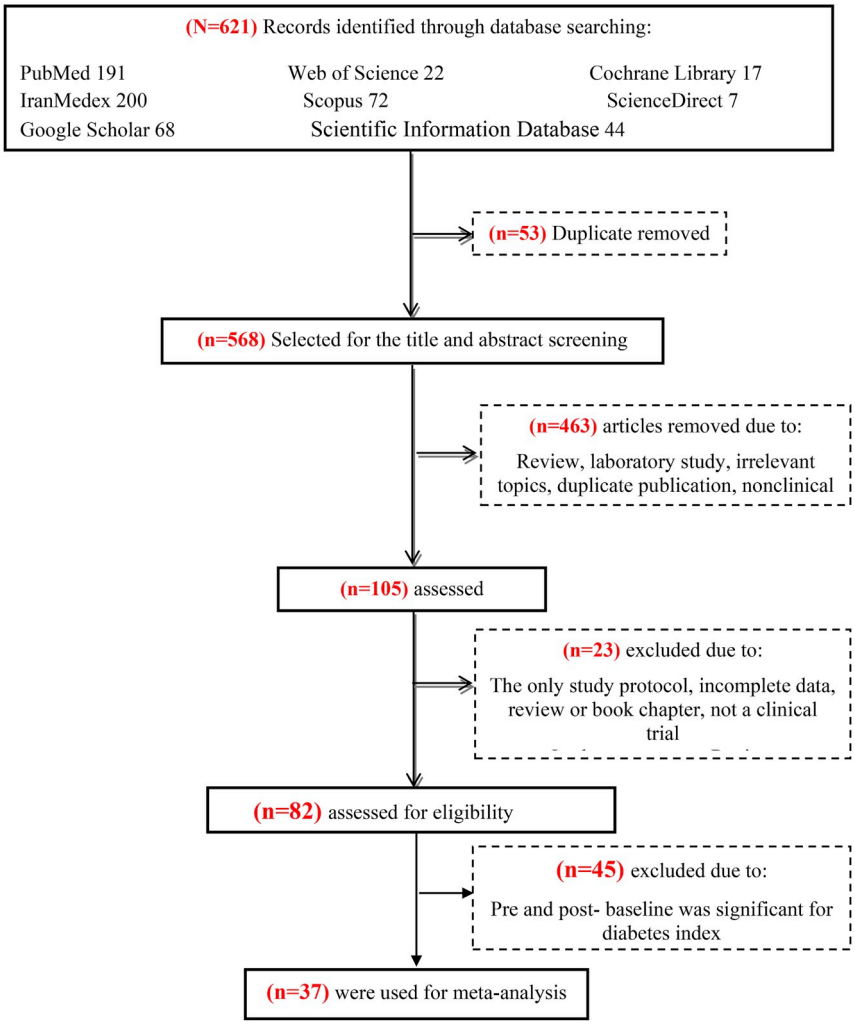


Fig. 1. Flow chart of literature search and study selection.

supplementation was associated with an improvement in lipid profile and insulin sensitivity by Quantitative Insulin-Sensitivity Check Index. The data for the cross-sectional and cohort studies are shown in Table 2. Unsurprisingly, FBG, HbA1C, and HOMA-IR were higher in the diabetic patient compared to healthy subjects, and serum vitamin D was lower in diabetics than in healthy controls.

3. Results

Fig. 3 shows the results of the meta-analysis for RCTs for FBG. The overall pooled results for the effects of vitamin D supplementation on FBG in GDM were not significant (p = 0.071, and 95% CI: −0.873 to 0.035) for GDM, but were significant in T2DM (p = 0.001, and 95% CI: −0.526 to −0.136). Although the relative weight of the study of Valizadeh et al. on GDM patients was higher than other studies, the result of this study was also non-significant (p = 0.119). Furthermore, the results of the sensitivity analysis showed that following the elimination of the study of Valizadeh et al. the final results were significant. Perhaps the high-dose vitamin D consumption and short-term follow up in Valizadeh's study in comparison with other studies may have been the cause of the lack of a significant result. Overall, vitamin D supplementation was associated with a significant improvement in FBG in diabetic patients (Fig. 3a and b).

Fig. 4 shows that vitamin D supplements had no significant effect on HbA1C in GDM (p = 0.199 and 95% CI: 3.270 to 0.681), but there was a significant effect on HbA1C in T2DM (p = 0.003 and 95% CI: 1.719 to −0.361). However, only the intervention study of Yazdchi in pregnant diabetic patients revealed significant effects, which may be due to factors such as the assessment of dietary intakes, use of matched categories regarding known confounders, sunlight exposure and pre-pregnancy BMI. Overall the final result was significantly in favor of intervention. This means that the intervention leads to a significant reduction in HbA1C in T2DM.

In Fig. 5, the study by Yazdchi et al. reported that vitamin D was not associated with an improvement in HOMA-IR, but overall, after increasing vitamin D intake, this did improve significantly (p = 0.028 and 95% CI: 0.924 to −0.053) in pregnant diabetic women. Also, vitamin D supplements were associated with a significant improvement in HOMA-IR (p = 0.005 and 95% CI: 1.772 to −0.319) in DM patients (Tables S1–S6).

In Fig. 6 the overall pooled result of cross-sectional meta-analysis indicated vitamin D level was lower (p = 0.018 and 95% CI: 0.587 to −0.054) in diabetic patients than for healthy controls (Table S7).

4. Discussion

We have undertaken a systematic review of the effects of dietary vitamin D on lipid profile, glycemic control and insulin resistance index in diabetic patients, that included GDM, T1DM, and T2DM. GDM affects approximately 4.7% of pregnant women in Iran [106]. Various factors, such as vitamin D deficiency and fast food intake are suggested as a risk factor for GDM [107,108]. In our systematic review, we found that

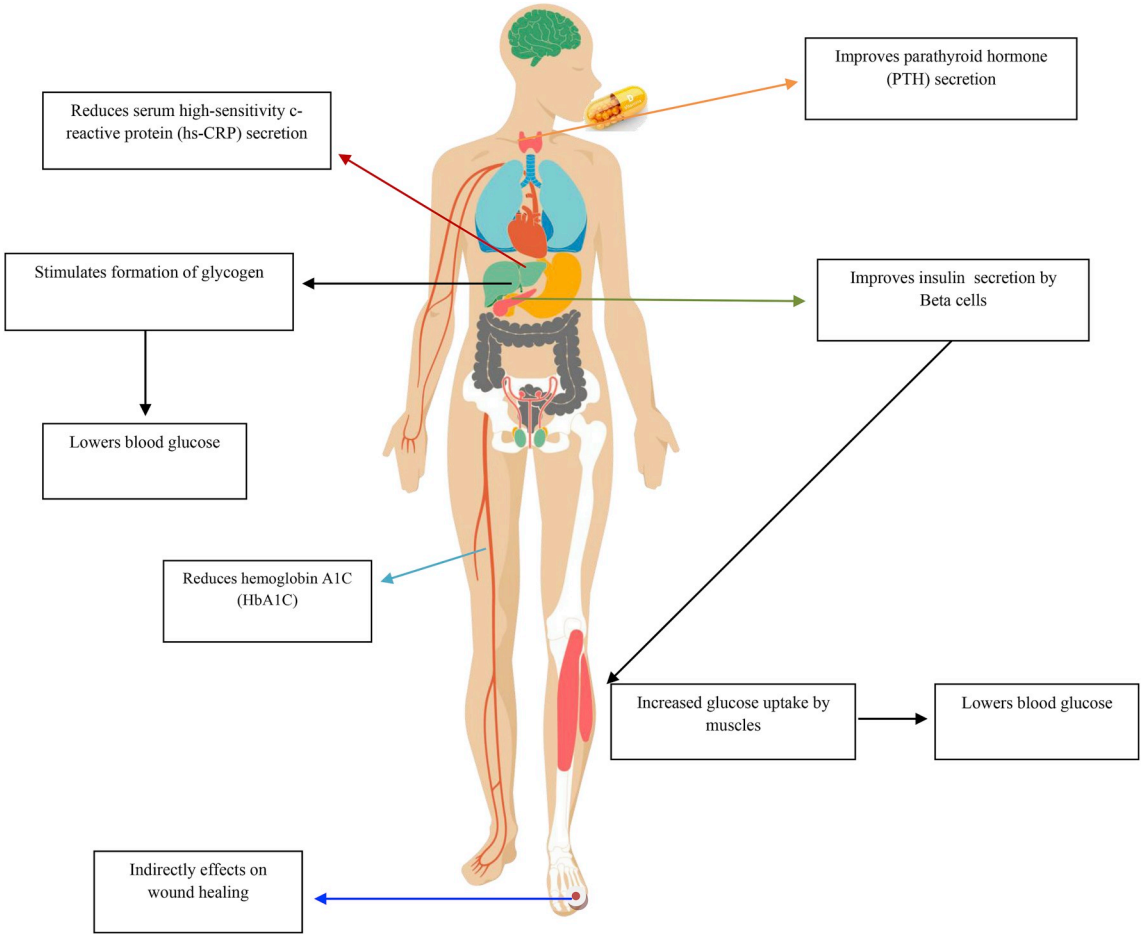


Fig. 2. The reported effects of vitamin D supplement in diabetics.

fasting plasma glucose (FPG) [80,83], HbA1C [81] and HOMA-IR were significantly higher in women with GDM, whereas serum insulin [81] and vitamin D levels [80] were lower compared with healthy control. Furthermore, vitamin D supplementation was associated with a significant reduction in HOMA-IR [36], FPG [44] and insulin [36] and an increase in QUICKI and sensitivity to insulin in the intervention group [40]. In agreement with previous studies, Shahgheibi et al. demonstrated, vitamin D supplementation intake has potentially beneficial effects as assessed by an improvement in glucose tolerance test (GTT) and reduction in the prevalence of GDM [39]. In a cohort study in Tehran, GDM subjects with postpartum metabolic syndrome had higher fasting glucose, and lower serum parathyroid hormone (PTH) than healthy control [84]. In some studies, vitamin D supplementation did not affect FPG [43], or insulin resistance [43] and there was no significant relationship between GDM with serum vitamin D levels [80,83]. Overall vitamin D consumption in women with GDM improved measures of glycemic status [36] and HbA1C levels and no complications have been reported [44]. Vitamin D plays a potentially important role in T1DM by suppressing activation of T-cells [97]. Although Ghandchi and co-workers report that FSG and HbA1C were higher in patients with T1DM compared to healthy control, serum vitamin D did not differ significantly between the subjects and unrelated non-diabetic controls. It has been proposed that vitamin D consumption in those who are genetically predisposed to the disease (i.e., siblings) may prevent T1DM [99]. Consumption of vitamin D supplements have a beneficial effect on HbA1C [48] and FBG in patients with T1DM and vitamin D insufficiency [46]. Ataie-Jafari et al. found that children with T1DM who are exposed to sunlight $\geq$15 min at weekends have a lower prevalence of vitamin D deficiency than T1DM children with $<$ 15 min exposure to sunlight. Because exposure to sunlight is an important source of vitamin D and also according to Ghandchi et al., vitamin D levels are important to the T helper 1 and T helper 2 balance and susceptibility to T1DM [47]. Saki at al observed the prevalence of vitamin D deficiency in boys with T1DM was lower than for girls [85]. Finally, we suggest that vitamin D supplementation could be an auxiliary treatment in patients with T1DM. According to the 8th International Diabetes Federation (IDF), the prevalence of T2DM in Iran is in excess of 4 million (8.43%) [109]. A low serum 25-hydroxy vitamin D [25(OH)D] has been associated with impaired glucose tolerance in T2DM [52]. The concentration of serum vitamin D is reported to be lower in diabetic patients than in healthy people [23,87,90,104,105]. Esteghamati et al. showed that vitamin D deficiency is associated with reduced insulin-producing in T2DM [101]. RCTs indicate that vitamin D supplements can improve serum vitamin D level [55], glycemic indicator [49,53,55,65,78], serum hs-CRP [53,68,69], lipid profile and HOMA-IR [49,55,60,72]. Furthermore, several studies have shown that HbA1C is reduced in intervention group compared to control group [53,60,64,72,110,111]. However, in some studies HbA1C was reduced in both groups. It is possible that the improvement in the control group was due to dietary change and taking plain doogh that contains calcium without vitamin D [61,112,113]. In contrast to these studies, Eftekhari and Jafari showed that HbA1C was increased in the intervention and control group [114,115] and in similarly Ahmadi et al. indicated HbA1C is increased in intervention group only. Moreover vitamin D supplementation for three months had no significant effect on reducing proteinuria in diabetic patients [70]. Some studies have demonstrated that dietary vitamin D intake reduces insulin in the intervention group [51,60,68,72,111,115–117]. Furthermore, Heshmat demonstrated the

Table 1
RCTs for the effects of vitamin D supplementation or vitamin D fortified food versus placebo, calcium or non-fortified food [25,31,33–79].

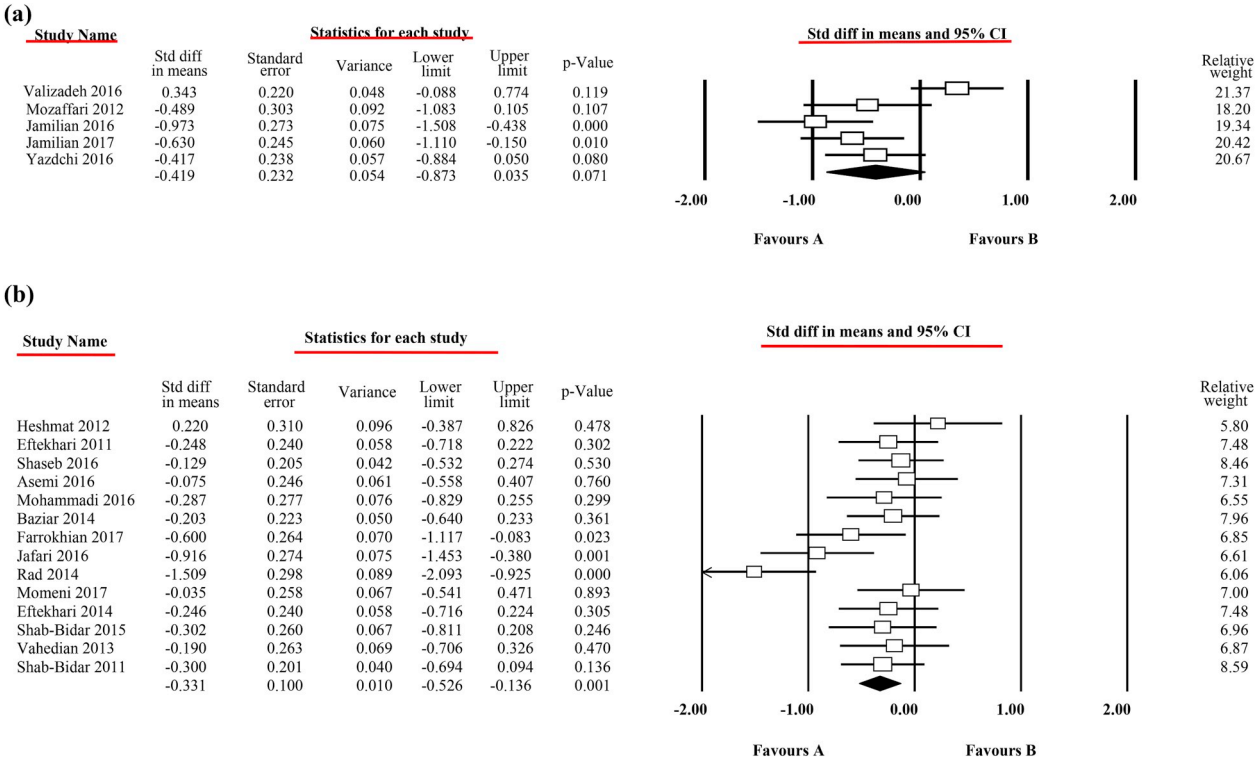
Ref.	City/ Sample size (n)	Type of diabetes	Serum Vitamin D assessment* (ng/ml)		Significant outcome	Non significant outcome
			Before	After		
[33-35]	Arak/260	GDM	15.2 ± 3.8	30.4 ± 4.1	FPG/ Insulin/ HOMA-IR HOMA-β / LDL cholesterol ↓	Serum Ca level ↑ HOMA-IR/ HOMA-β TC/TAG ↓
[36-38]	Kashan/155	GDM	17	30	FPG/ Serum insulin HOMA-IR ↓	Insulin resistance LDL/ TC hs-CRP ↓
[39]	Sanandaj/90	GDM	13.5	Not reported	GCT/ GTT ↓	Not reported
[40-42]	Yazd/560	GDM	21.1	52	FBG/ 1-h OGTT / PTH ↓	QUICKI Insulin sensitivity HbA1C ↑ FPG ↓
[43]	Zanjan/84	GDM	14.6	32.4	Not reported	HbA1C/ HOMA-IR ↑
[44]	Tabriz/72	GDM	6.12±15.94	24.70± 37.94	FBG/ HbA1C ↓	Not reported
[45]	Isfahan/210	GDM	Not reported		Not reported	Vitamin D cannot prevent the incidence of gestational diabetes
[46]	Gorgan/47	T1DM	Not reported		HbA1C ↓	Not reported
[47]	Tehran/53	T1DM	14	Not reported	Not reported	Vitamin D deficiency in boys was lower than girls in this model
[48]	Yazd/65	T1DM	Not reported		FBG/ HbA1C ↓	Not reported
[49]	Arak/100	T2DM	43.03±19.28	60.12±17.2	Not reported	1. Insulin 2. HOMA-IR 3.Serum FPG ↓
[25, 50-63]	Tehran/1585	T2DM	33.69	49.84	Insulin/ TG/ TC/ MMP-9 FSG/ HbA1C / hs-CRP HOMA-IR/ IL-1/ IL-6 Fibrinogen / TNF-α ↓ Apo A1/ Apo B/ GSH ↑	QUICKI/ MDA/ Cardiac myeloperoxidase(MP)/ SOD ↓
[64]	Urmia/51	T2DM	21.46±4.65	46.39±6.89	TNF-α/ HbA1C ↓	Serum leptin ↑
[65, 66]	Shiraz/140	T2DM	43.3±32.1	34.1±31.5	Not reported	LDL/ HDL/ TC/ TG FBG ↓ Level of insulin ↑
[67]	Qom/120	T2DM	Not reported		HOMA-IR ↓	Not reported
[68, 69]	Kashan/126	T2DM	16	28	Insulin/ HOMA-IR/ HOMA-β / hs-CRP ↓	FPG ↓
[31, 70-75]	Isfahan/595	T2DM	15.23	38.27	SBP/ HbA1C/ Serum insulin/ HOMA-IR LDL-cholesterol/ HOMA-β / IL-6/ TNF-α ↓	HbA1C/ GFR/ Serum Ca/P ↑ BUN/ Serum Cr/ UACR/ FSG ↓
[76]	Yazd/53	T2DM	19	69	Insulin/ Insulin resistance ↓	FBG ↓
[77-79]	Shahrekord/ 180	T2DM	18	35	SBP/ DBP ↓	Proteinuria/ HbA1C ↓ FBG ↑

*The mean concentration of vitamin D (before and after intervention) is shown in the study for each city; GDM: gestational diabetes mellitus; HbA1C: hemoglobin A1C; T1DM: Type 1 diabetes mellitus; HOMA- β: Homeostatic Model Assessment β-cell function; T2DM: Type 2 diabetes mellitus; FPG: fasting plasma glucose; HOMA-IR: Homeostatic Model Assessment Insulin Resistance; LDL: low-density lipoprotein; Ca: Calcium; Cr: Chromium; TC: total cholesterol; TAG: triacylglyceride; FBG: fasting blood glucose; hs-CRP: high-sensitivity C-Reactive Protein; GCT: Glucose Challenge Test; GTT: Glucose Tolerance Test; 1-h OGTT: 1 h oral glucose tolerance test; PTH: Parathyroid Hormone; QUICKI: Quantitative Insulin-Sensitivity Check Index; MMP-9: matrix metalloproteinase 9; FSG: fasting serum glucose; TNF-α: tumor necrosis factor alpha; MDA: Malondialdehyde; SOD: superoxide dismutase; GSH: Glutathione; APO: Apolipoprotein; IL: Interleukin; HDL: High-Density Lipoprotein; GFR: glomerular filtration rate; SBP: systolic blood pressure; DBP: diastolic blood pressure; BUN: blood urea nitrogen; P: phosphate; UACR: urine albumin/creatinine ratio; ↑: Increased level; ↓ decreased level.

Table 2
The cross-sectional and Cohort studies for the effects of vitamin D supplementation or vitamin D fortified food versus placebo, calcium or non-fortified food [23,80–105].

Reference	City/ Sample size	Type of diabetes	Significant outcome	Non significant outcome
[80]	Yazd/204	GDM	Not reported	FSG ↑
[81]	Shahrekord/155	GDM	Insulin ↓	FBG/ HbA1C ↑
[82]	Ahvaz/90	GDM	Not reported	Fasting blood Insulin/ TNF-α hs-CRP/ HOMA-IR/ FBG ↑
[83]	Tabriz/136	GDM	FBG/ GTT 1h/ GTT 2h ↑	Not reported
[84]	Tehran/303	GDM	Fasting glucose ↑	Fasting insulin/ C-peptide/ ff genotype ↑ PTH ↓
[85]	Shiraz/85	T1DM	Not reported	FBG/ HbA1C/ Ca ↑
[23, 86-89]	Tehran/776	T2DM	FBG/ TG ↓ HbA1C/ HOMA-IR/ FBG ↑	Insulin/ PTH/ HbA1C Serum P/ Serum Ca ↓ PTH ↑
[90-92]	Mashhad/473	T2DM	hs-CRP/ GFR ↓	FBG/ HbA1C/ TG/ Insulin ↓
[93]	Ahvaz/84	T2DM	HbA1C/ hs-CRP ↑	TNF-α/ FBG ↑
[94]	Zanjan/375	T2DM	Not reported	Insulin/ HOMA-IR/ LDL ↑ FPG ↓
[95]	Shahrekord/36	T2DM	25-hydroxyvitamin D level in none-diabetic ↓	Not reported
[96]	Arak/314	GDM	FBG/ 1hPPG/ 2hPPG ↑	The CC genotype of VDR ApaI polymorphism increased the risk of GDM
[97, 98]	Mashhad/301	T1DM	Not reported	frequencies of 3 genotypes (*Aa, FF,* and *Bb*) ↑
[99]	Tehran/180	T1DM	FSG and HbA1C ↑	Not reported
[100-102]	Tehran/3016	T2DM	SBP ↑ Tt genotype of the VDR Gene presented a significantly higher FBG than those with TT and tt genotypes in TaqI polymorphisms	DBP/ FPG/ HbA1C HOMA-IR ↑ HOMA-β ↓
[103]	Rafsanjan/200	T2DM	The frequency of Polymorphisms Within Intron 8 and Exon 9 of the VDR Gene in T2D Patients compared with HC: Tt/ Aa ↑	Not reported
[104]	Babol/240	T2DM	Not reported	The mean concentration of vitamin D in women with diabetes was lower than the healthy women
[105]	Zahedan/100	T2DM	Not reported	BMI ↓

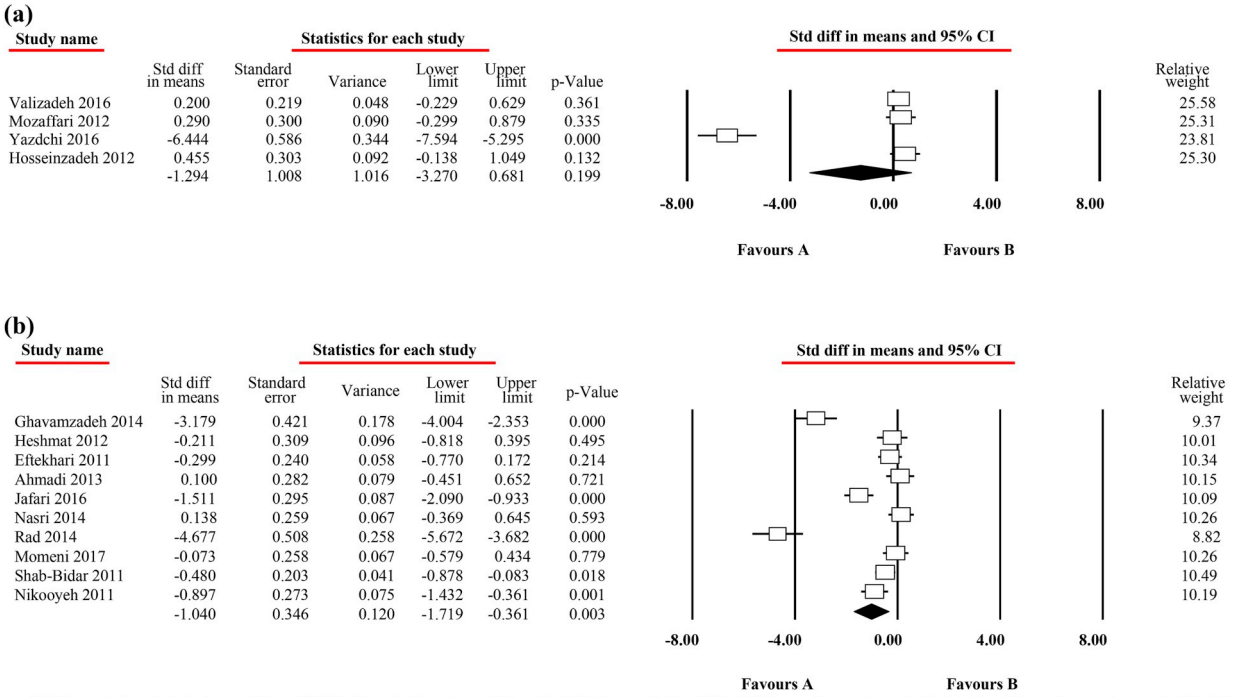
GDM: gestational diabetes mellitus; T1DM: Type 1 diabetes mellitus; T2DM: Type 2 diabetes mellitus; FPG: fasting plasma glucose; DBP: diastolic blood pressure; HbA1C: hemoglobin A1C; HOMA-IR: Homeostatic Model Assessment Insulin Resistance; Ca: Calcium; hs-CRP: high-sensitivity C-Reactive Protein; LDL: Low-Density Lipoprotein; GTT: Glucose Tolerance Test; FBG: Fasting blood glucose; PTH: parathyroid hormone; FSG: fasting serum glucose; TNF-α: Tumor Necrosis Factor-alpha; VDR: vitamin D receptor; APO: apolipoprotein; SBP: systolic blood pressure; P: phosphate; PPG: post prandial glucose; HOMA- β: Homeostatic Model Assessment β-cell function; BMI: body mass index; GFR: glomerular filtration rate; HC: Healthy control; ↑: Increased level; ↓ decreased level.



GDM: gestational diabetes mellitus; T2DM: Type 2 diabetes mellitus; FBG: fasting blood glucose; RCTs: randomized controlled trials; CI: confidence interval; Std diff in means: standard difference in means.

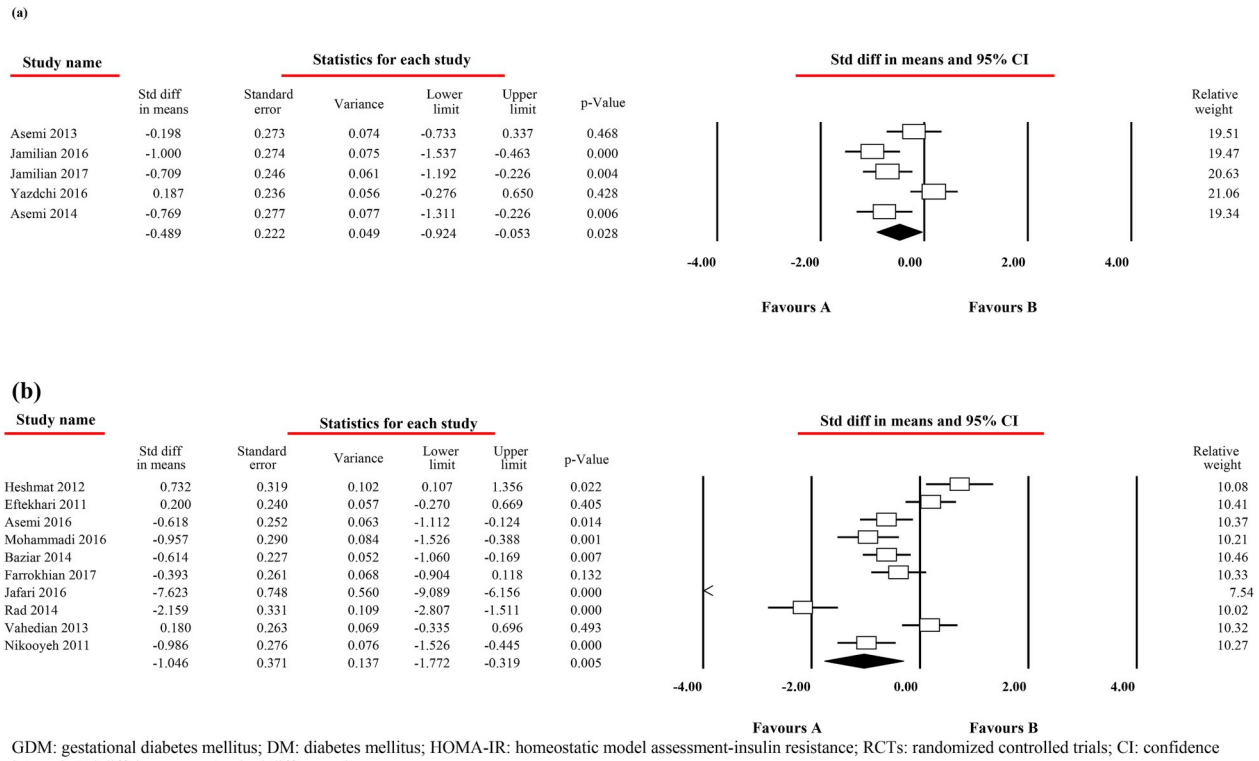
Fig. 3. Forest plots of the association between intake of vitamin D and FBG in RCTs (a) GDM and (b) T2DM studies. The centre of each square indicates the horizontal line indicates the 95% CI; the area of the square is proportional to the amount of information from that study; diamonds are pooled estimates.

consumption of vitamin D plus calcium is more effective compared with intake vitamin D only to decrease the risk of T2DM [51]. Following some previous studies, Mohammadi showed that vitamin D supplementation leads to a significant reduction to insulin resistance in the intervention group [76]. In some studies, calcium plus vitamin D supplements have been shown to have a positive effect on BMI, hip circumference and systolic blood pressure in subjects with T2DM [71,72]. Hoseini et al. observed that the intake of vitamin D supplements did not



GDM: gestational diabetes mellitus; T2DM: Type 2 diabetes mellitus; HbA1C: hemoglobin A1C; RCTs: randomized controlled trials; CI: confidence interval; Std diff in means: standard difference in means.

Fig. 4. Forest plots of the association between intake of vitamin D and HbA1C in RCTs (a) GDM and (b) T2DM diabetes studies.



GDM: gestational diabetes mellitus; DM: diabetes mellitus; HOMA-IR: homeostatic model assessment-insulin resistance; RCTs: randomized controlled trials; CI: confidence interval; Std diff in means: standard difference in means.

Fig. 5. Forest plots of the association between intake of vitamin D and HOMA-IR in RCTs (a) GDM and (b) DM diabetes studies.

effect on insulin sensitivity, however it caused a reduction in FPG and HbA1C, that was increased in pre-diabetic subjects [118].

4.1. Vitamin D fortification studies

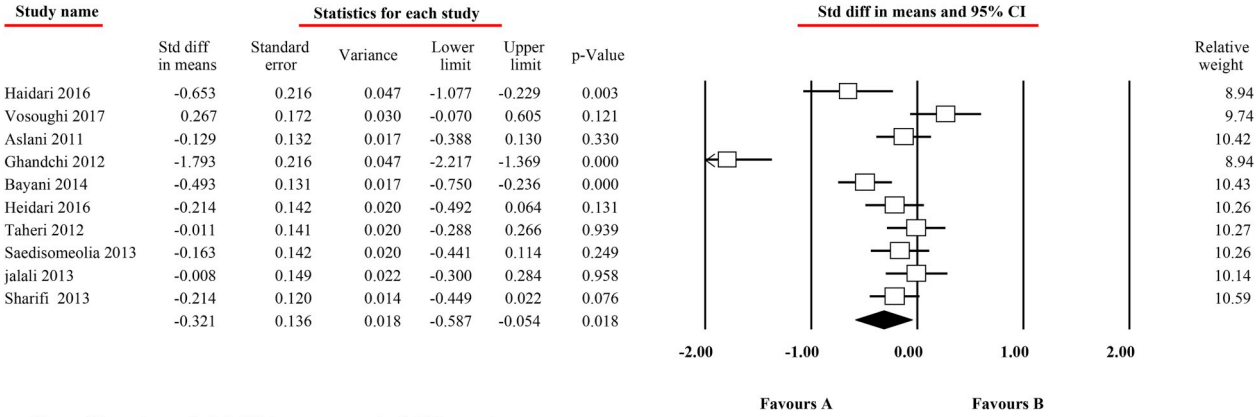
The main source of vitamin D in humans is from synthesis in the skin. Factors such as the duration of exposure, latitude, season, senescence, skin pigmentation and the continued use of sunscreens can affect the synthesis of vitamin D [119]. Although fortification of foods with vitamin D is not usual in Iran, some research has led to the proposal that the daily intake of a vitamin D should be increased by fortified yogurt drink, either with or without added calcium, improved glycemic status in T2DM patients [31,52,120]. Nikooyeh and Shab-bidar showed, serum glucose, HbA1C, HOMA–IR, oxidative stress (OS) [85,86] and insulin improved after vitamin D–fortified yogurt drink and vitamin D plus calcium–fortified yogurt drink intaking in the intervention group [52]. Furthermore, Hajmohammadi et al. have suggested vitamin D3-fortified doogh compared with plain doogh leads to a reduction in serum hs-CRP and parathyroid hormone (PTH) concentrations [58].

4.2. Vitamin D and diabetic neuropathy

Diabetic neuropathy (DN) is the most common complication of DM and also a major cause of morbidity and mortality in diabetic patients. Alamdari et al. in a cross-sectional study, observed reduction the levels of circulating 25(OH)-D was associated with an increased risk of large fiber neuropathy and FBG in type2 diabetic people [121]. In other research, Esteghamati et al. suggested an intake of vitamin D should be done more carefully, particular in diabetic subjects. As well as results showed FPG and HbA1C were increased in DN [122].

4.3. Vitamin D & diabetic foot ulcer

Diabetic foot ulcer (DFU) is known as one serious vascular



CI: confidence interval; Std diff in means: standard difference in means.

Fig. 6. Forest plot of the comparison between vitamin D level in Diabetic patients and Healthy control.

complications of diabetes. Razzaghi indicated, in diabetic patients with foot ulcer, vitamin D supplementation intake caused to improve glucose homeostasis, lipid profiles, decreases HbA1C and FPG. They suggested, improve glucose homeostasis had indirectly beneficial effects on wound healing [123]. Pooled data from all studies suggested, intake vitamin D supplement and vitamin D3-fortified doogh/yogurt improve several factors in diabetic patients after intervention. In Fig. 2, some of the effects of vitamin D on diabetics have been shown.

4.4. Strengths and limitations

This review is the first meta-analysis assessing the effect of vitamin D on glycemic indices in diverse subgroups of diabetes and also, summarizes cross-sectional, cohort and interventional studies in diabetic patients. However, it should be noted that a major limitation of our study is the lack of pre and post-baseline measures for glycaemic indices in several papers, requiring them to be excluded from the meta-analysis.

5. Conclusion

This systematic and meta-analysis review demonstrated that vitamin D had major effects on FBG of type 2 diabetics and pregnant women with diabetes. Therefore, vitamin D could be used as an adjuvant therapy along with the other treatments for those patients. Also, vitamin D supplementation leads to an improvement in HOMA-IR, FBG, and HbA1C. Furthermore, the overall pooled result of the cross-sectional meta-analysis showed the level of vitamin D is lower in diabetic patients than healthy control significantly. However, further studies are required to better understand the relationship between vitamin D supplementation and glucose homeostasis indexes in type 2 diabetes patients and pregnant diabetic women.

Conflicts of interest

The authors disclose no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctcp.2018.12.009.

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