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The Effects of Vitamin D Supplementation on Biomarkers of Inflammation and Oxidative Stress in Diabetic Patients: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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ABSTRACT

In this systematic review and meta-analysis of randomized controlled trials (RCTs), the effects of vitamin D supplementation on biomarkers of inflammation and oxidative stress in diabetic patients are summarized. The following databases were searched up to December 2017: MEDLINE, EMBASE, Web of Science, and Cochrane Central Register of Controlled Trials. The quality of the relevant extracted data was assessed according to the Cochrane risk of bias tool. Data were pooled using the inverse variance method and expressed as mean difference with 95 % Confidence Intervals (95 % CI). Heterogeneity between studies was assessed by the Cochran Q statistic and I-squared tests (I^2). Overall, 33 studies were included in the meta-analyses. Vitamin D supplementation were found to significantly reduce serum high-sensitivity C-reactive protein (hs-CRP) (WMD 0.27; 95 % CI, – 0.35, – 0.20; p < 0.001) and malondialdehyde (MDA) levels (WMD – 0.43, 95 % CI – 0.62, – 0.25, p < 0.001) in diabetic patients. In addition, vitamin D supplementation were found to increase markers of nitric oxide (NO) release (WMD 4.33, 95 % CI 0.96, 7.70), total serum antioxidant capacity (TAC) (WMD 57.34, 95 % CI 33.48, 81.20, p < 0.001) and total glutathione (GSH) levels (WMD 82.59, 95 % CI 44.37, 120.81, p < 0.001). Overall, this meta-analysis shows that in diabetic patients, taking vitamin D had significant effects on hs-CRP and MDA levels, and significantly increased NO, TAC and GSH levels.

Abbreviations

GSH	Total glutathione
hs-CRP	High-sensitivity C-reactive protein
MDA	Malondialdehyde
NO	Nitric oxide
TAC	Total antioxidant capacity

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Introduction

Diabetes mellitus is a group of metabolic disorders characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both, and is associated with long-term damage, and failure of several organs, including the kidney, nerves, heart, and blood vessels [1]. The International Diabetes Federation (IDF) projections of the prevalence of type 2 diabetes mellitus (T2DM) and prediabetes are expected to reach 592 million individuals globally and 471 million by 2035, respectively [2]. Several studies have documented that a decrease in antioxidative levels and an elevation in anti-inflammatory and oxidative stress biomarkers might be involved in the pathophysiology of cognitive disorder associated with diabetes [3, 4] and cardiovascular diseases (CVD) [5].

Several studies have demonstrated that vitamin D intake may reduce the inflammatory response and oxidative stress [6, 7]. Therefore, hypovitaminosis D has been suggested to contribute to various metabolic-related conditions including insulin resistance [8], diabetes [9], and CVD [10]. Furthermore, biomarkers of inflammation and oxidative stress have been shown to be high in people with low vitamin D 25(OH)D levels; however, the reports have been inconsistent [11, 12]. In a previous meta-analysis, vitamin D administration was found to be beneficial for the reduction of circulating high-sensitivity C-reactive protein (hs-CRP) levels [13]. However, in another meta-analysis study conducted in the obese and overweight people, supplementation with vitamin D did not have a significant impact on changes in selected inflammatory biomarkers levels [14]. Recently, a number of clinical trials evaluating vitamin D administration on different populations have been performed to determine if circulating levels of inflammatory markers and biomarkers of oxidative stress are affected among diabetic patients [15–18]. However, the sample size of these trials was small, the quality of the studies was variable, and the results were inconsistent.

Despite several randomized controlled trials (RCTs), we are aware of no systematic review and meta-analysis of RCTs on the effect of vitamin D supplementation on biomarkers of inflammation and oxidative stress among diabetic patients. This current meta-analysis was conducted to summarize the available evidence of RCTs to establish the effect of vitamin D supplementation on biomarkers of inflammation and oxidative stress among diabetic patients.

Materials and Methods

Search strategy and selection studies

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline were conformed to design, analysis, and reporting of this study [19]. Eligible RCTs were identified using Cochrane Library, Embase, Medline, and Web of Science databases for relevant articles published until December 2017, and by manually searching the reference list of the retrieved articles. Databases of International Standard Randomized Controlled Trial Number Register and Meta-register for RCTs were also searched for all ongoing trials. Studies retrieved that evaluated the effects of vitamin D supplementation on biomarkers of inflammation and oxidative stress by using the following MeSH and text words: patients [“diabetes”], intervention [(“vitamin D3 and/or D2” OR “vitamin D supplement” OR “vitamin D treatment” AND “supplementation” OR “intake”)], and outcomes [“hs-CRP” OR “malondialdehyde (MDA)” OR “nitric oxide (NO)” OR “total glutathione (GSH)” OR “total antioxidant capacity (TAC)”] to December 2017. The search was limited to studies in humans and published in English. Additional manual search such as reference lists of related studies; former review studies were reviewed to increase sensitivity in search strategy. One author (VO) independently read the abstracts of all identified studies to exclude those that were clearly not relevant. The full texts of the remaining articles were read to determine if they met the study inclusion criteria. In case of discrepancy, consensus was reached or resolved by discussion with a third author (ZA). Trials were included for meta-analysis that met the following criteria: 1) original trials, 2) human trials, 3) intervention and control groups received of vitamin D supplementation and placebo, respectively, and 4) the trials reported mean changes or mean difference of body composition and/or metabolic profiles with standard deviation (SD) for the intervention and control groups.

Data extraction and quality assessment

Two authors (VO and AD) independently extracted data and have assessed the quality of all RCTs by using standard forms and the Cochrane Collaboration risk of bias tool [20, 21], respectively. This tool is based on information on the following domains: randomization generation, allocation concealment, blinding of subjects and outcome assessment, incomplete outcome data, and selective outcome reporting, and other sources of bias. When there was disagreement among them, it was resolved by discussion with the third author (ZA). Eligible studies were reviewed and the following data were abstracted: 1) first authors’ name, 2) publication year, 3) age, sex, and body composition and/or metabolic profiles of study participants and associated measures of variance, 4) study location, 5) number of participants in the intervention and control groups, 6) study design, and 7) duration of the intervention.

Data analysis

Heterogeneity and publication biases

The statistical heterogeneity across the results of the included studies was tested using chi-square test at the 5 % significant level [22], and quantified by the I^2 statistic [23]. Meta-regression was used for assessing the source of heterogeneity. Publication bias was assessed by the funnel plot and tested for statistical significance using the Egger’s test [24].

Summary measures

We calculated the mean difference for the effect of vitamin D supplementation on biomarkers of inflammation and oxidative stress for each included studies. The change score approach was used to obtain the effect sizes, because the correlations between baseline and end measurements were more than 1/2 [25]. A meta-analysis was performed to obtain the summary measures for the effect of vitamin D supplementation on biomarkers of inflammation and oxidative stress using the inverse variance method. The random effects model was used to report the pooled mean difference with 95 % confidence interval (CI). p-Values < 0.05 were considered as statistically significant. Statistical analyses were performed using Stata version 11.0 (Stata Corp., College Station, TX, USA).

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Results

Description of the included RCTs

Our initial search found 1053 potential citations. After screening, 33 trials were proven to be eligible for meta-analysis. ▶ **Fig. 1** shows the details of step-by-step study identification and selection. The key characteristics of the RCTs are summarized in ▶ **Table 1**. Trials were published between 2012and 2017. These 33 selected studies included 1053 randomized participants. The quality of the included trails was assessed as described in the Cochrane Handbook for Systematic Reviews of Interventions and the results of risk of bias are summarized in ▶ **Fig.1**.

Main outcomes

The effects of vitamin D supplementation on inflammatory markers

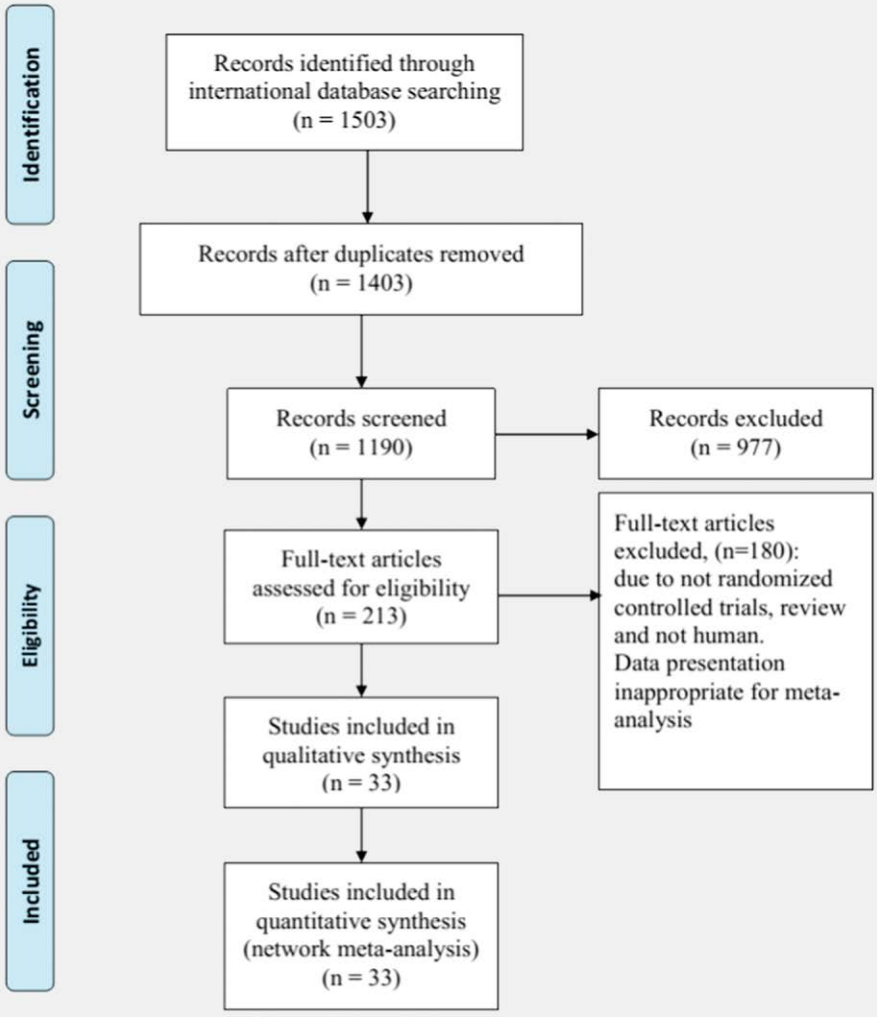
The findings showed that vitamin D supplementation significantly reduced serum hs-CRP [WMD – 0.27 (– 0.35, – 0.20); p < 0.001], and significantly increased NO [WMD 4.33 (0.96, 7.70), p < 0.001] in diabetic patients (▶ **Fig. 2**, **4**). The results of subgroup analysis of the effect of vitamin D supplementation based on the type of disease are shown in ▶ **Fig. 3**.

The effects of vitamin D supplementation on biomarkers of oxidative stress

Vitamin D supplementation also significantly reduced serum MDA levels [WMD – 0.43 (– 0.62, – 0.25), p < 0.001], (▶ **Fig. 7**) and TAC [WMD 57.34 (33.48, 81.20), p < 0.001] (▶ **Fig. 5**), and GSH levels [WMD 82.59 (44.37, 120.81), p < 0.001] in diabetic patients (▶ **Fig. 6**).

Heterogeneity and publication bias

The results of the chi-square test showed that there was considerable heterogeneity across the results of the included RCTs. The I^2 for studies assessed the effect of vitamin D supplementation on hs-CRP, NO, TCA, GSH, and MDA levels were 92.5 % (p < 0.001), 94.0 % (p < 0.001), 65.5 % (p < 0.001), 98.1 % (p < 0.001), and 73.5 % (p = 0.01), respectively (▶ **Fig. 2,4–7**). Based on the results of meta-regression analysis, the type of disease had a significant association with the heterogeneity for the effect of vitamin D supplementation on hs-CRP levels (p = 0.01).



▶ **Fig. 1** Literature search and review flow-chart for selection of studies.

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▶ **Table 1** Characteristics of the studies included in the analysis.

Authors [Ref.]	Year	Location	Sample size	Duration (week)	Subject type	Age (years)	Intervention (name and daily dose)
Breslavsky et al. [49]	2013	Israel	47	12 months	T2DM	65.8 ± 9.7, 66.8 ± 9.2	1000 IU vitamin D3/day
Kampmann et al. [50]	2014	Denmark	15	12 weeks	T2DM	57.0 ± 4.5, 61.6 ± 4.4	11 200 IU vitamin D3 daily for 2 weeks, followed by 5600 IU Vitamin D3 daily for 10 weeks
Yiu et al. [51]	2013	Hong Kong	100	12 weeks	T2DM	64.9 ± 8.9, 65.8 ± 7.3	5000 IU vitamin D3/day
Shab-Bidar et al. [52]	2012	Iran	100	12 weeks	T2DM	52.6 ± 6.3 , 52.4 ± 8.4	1000 IU vitamin D3 + 340 mg calcium/day
Tamadon et al. [7]	2018	Iran	60	12 weeks	Diabetic hemodialysis	65.1 ± 10.1, 60.1 ± 10.4	50 000 IU vitamin D3 every 2 weeks
Eftekhari et al. [41]	2013	Iran	70	12 weeks	T2DM	52.4 ± 7.8, 53.8 ± 8.9	0.5 µg dihydroxycholecalciferol (calcitriol)/day
Asemi et al. [53]	2013	Iran	54	6 weeks	GDM	31.8 ± 6.6, 31.7 ± 5.6	50 000 IU vitamin D3 at baseline and at day 21 of the intervention
Asemi et al. [54]	2014	Iran	56	6 weeks	GDM	30.8 ± 6.6, 28.7 ± 6.0	50 000 IU vitamin D3 at baseline and at day 21 of the intervention + 1 g calcium/day
Asemi et al. [55]	2016	Iran	66	12 weeks	T2DM with CHD	65.0 ± 11.1, 65.9 ± 11.4	400 IU vitamin D3 + 1 g calcium + 180 µg vitamin K/day
Mustafar et al. [56]	2014	Malaysia	31	12 weeks	Diabetic CKD	52.0 (20.5), 55 (9.5)	0.5 µg dihydroxycholecalciferol (calcitriol) + 500 mg calcium/day
Farrokhian et al. [40]	2017	Iran	60	6 months	T2DM with CHD	63.0 ± 10.7, 60.5 ± 8.6	50 000 IU vitamin D3 every 2 weeks
Razavi et al. [57]	2017	Iran	60	6 weeks	GDM	29.2 ± 3.4, 29.9 ± 5.0	50 000 IU vitamin D3 every 2 weeks
Razavi et al. [57]	2017	Iran	60	6 weeks	GDM	29.2 ± 3.4, 29.9 ± 4.0	50 000 IU vitamin D3 every 2 weeks + 2 g omega-3/day
Neyestani et al .[58]	2017	Iran	60	12 weeks	T2DM	50.8 ± 6.7, 51.5 ± 5.4	500 IU vitamin D3 + 150 mg calcium/day
Neyestani et al .[58]	2011	Iran	60	12 weeks	T2DM	50.8 ± 6.7, 49.9 ± 6.2	500 IU vitamin D3 + 250 mg calcium/day
Razzaghi et al. [59]	2016	Iran	60	12 weeks	DFU	58.6 ± 8.6, 59.6 ± 8.2	50 000 IU vitamin D3 every 2 weeks
Shaseb et al. [60]	2016	Iran	95	8 weeks	T2DM	55.89 ± 5.24, 54 ± 6.13	300 000 IU vitamin D3 (single dose, IM)
Shab-Bidar et al. [61]	2014	Iran	100	12 weeks	T2DM	52.4 ± 8.4, 52.6 ± 6.3	1000 IU vitamin D3/day

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▶ **Table 1** Continued

Authors [Ref.]	Year	Location	Sample size	Duration (week)	Subject type	Age (years)	Intervention (name and daily dose)
Barchetta et al. [62]	2016	Italy	55	24 weeks	T2DM	59.8 ± 9.1, 57.4 ± 10.7	2000 IU vitamin D3/day
Munisamy et al. [63]	2016	Malaysia	60	6 months	T2DM	56.22 ± 7.03, 57.57 ± 6.71	0.25 µg alfacalcidol/day
Jafari et al. [64]	2016	Iran	59	12 weeks	T2DM	56.8 ± 5.7, 57.8 ± 5.5	2000 IU vitamin D3/day (fortified yogurt)
Sadiya et al. [65]	2015	United Arab Emirates	82	6 months	T2DM	48 ± 8, 49 ± 8	6000 IU vitamin D3/day for 3 months followed by 3000 IU vitamin D3/day
Yazdchi et al. [66]	2016	Iran	72	2 months	GDM	32.1 ± 3.61, 31.64 ± 4.40	50 000 IU vitamin D3 every 2 weeks
Thethi et al. [67]	2015	USA	46	12 weeks	T2DM with CKD	61.0 (51.0–71.0) , 64 (53.071.0)	1 µg paricalcitol/day
Tabesh et al. [68]	2014	Iran	59	8 weeks	T2DM	51.0 ± 6.1, 50.2 ± 6.6	50 000 IU vitamin D3 per week
Ryu et al. [69]	2014	Korea	62	24 weeks	T2DM	56.7 ± 7.9, 54.5 ± 7.4	2000 IU vitamin D3 + 200 mg calcium/day
Jehle et al. [70]	2014	Switzerland	55	6 months	T2DM	63.7 ± 3.5, 66.9 ± 3.1	300 000 IU vitamin D3 (single dose, IM)
Akbarzadeh et al. [71]	2013	Iran	70	3 months	T2DM	52.4 ± 7.8, 53.8 ± 8.9	0.5 µg dihydroxycholecalciferol (calcitriol)/day
Nikooyeh et al. [72]	2014	Iran	60	12 weeks	T2DM	50.8 ± 6.7, 51.5 ± 5.4	500 IU vitamin D3 + 150 mg calcium/day
Nikooyeh et al. [72]	2014	Iran	60	12 weeks	T2DM	50.8 ± 6.7, 49.9 ± 6.2	500 IU vitamin D3 + 250 mg calcium/day
Zhang et al. [73]	2016	China	57	24–28 weeks of pregnancy until delivery	GDM	29.8 ± 4.7, 30.1 ± 4.5	50 000 IU vitamin D3 every 2 weeks (high dose)
Zhang et al. [73]	2016	China	58	24–28 weeks of pregnancy until delivery	GDM	29.8 ± 4.7, 29.4 ± 4.9	50 000 IU vitamin D3 monthly (medium dose)
Zhang et al. [73]	2016	China	58	24–28 weeks of pregnancy until delivery	GDM	29.8 ± 4.7, 30.3 ± 5.1	200 IU vitamin D3/day (low dose)

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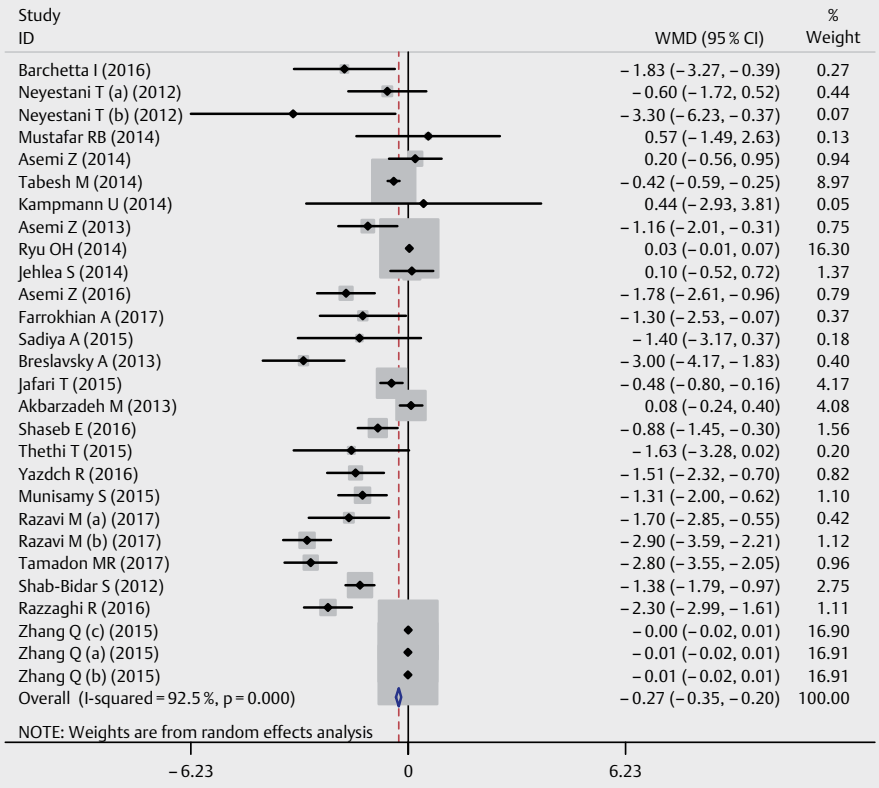

▶ **Fig. 2** Forest plot of the mean difference for the effect of vitamin D supplementation on serum hs-CRP levels in diabetic patients.

The possibility of publication bias was assessed using a funnel plot (▶ **Fig. 8),** and Egger's test. In ▶ **Fig. 8a**, the RCTs scattered asymmetrically around the null vertical line, indicating publication bias for the effect of vitamin D supplementation on hs-CRP ($p < 0.001$), and MDA ($p = 0.04$) (▶ **Fig. 8d**). For the effect of vitamin D supplementation on TAC ($p = 0.28$) and GSH ($p = 0.43$) there was no evidence of publication bias (▶ **Fig. 8b and c**).

Discussion

This systematic review and meta-analysis is the first report of the effect of vitamin D supplementation on biomarkers of inflammation and oxidative stress among diabetic patients. This meta-analysis showed that taking vitamin D significantly reduced serum hs-CRP and MDA levels (markers of inflammation and oxidative stress respectively), and significantly increased NO, TAC, and GSH levels.

Diabetic patients appear to be susceptible to increased biomarkers of inflammation and oxidative stress [26]. This meta-analysis demonstrated that vitamin D supplementation resulted in a significant decrease in hs-CRP and a significant increase in NO levels in diabetic patients. Vitamin D deficiency is a common status affecting over 40 % of the United States population [27]. Deficiency in 25-hydroxyvitamin D levels has been independently correlated with increased risk of CVD, severity of coronary atherosclerosis, and all-cause mortality [28, 29]. The potential anti-inflammatory effects of vitamin D have been widely reported in previous studies [30, 31]. In a meta-analysis study conducted by Chen et al. [13], it was shown that vitamin D supplementation significantly reduced serum hs-CRP concentrations. In addition, vitamin D supplementation to women with polycystic ovary syndrome led to an improvement in hs-CRP, MDA and TAC, but did not influence NO and GSH levels [32]. In this study, individuals had much higher levels of inflammation, with baseline circulating CRP concentrations varying from 1.71 to 22 mg/l (median of 5 mg/l) [14]. In addition, cross-sectional studies have documented the negative association between circulating vitamin D levels and inflammatory factors in some groups. For instance, an inverse association between serum 25(OH)D concentrations and inflammatory markers was observed in older individuals from the general population [33]. Moreover, an inverse relation was documented in 147 morbidly obese people whose hs-CRP concentrations ranged from 1.88 to 4.01 mg/l [34]. Unlike, another meta-analysis study among overweight/obese people found no significant impact of cholecalciferol and ergocalciferol administration on inflammatory markers [14]. Increased systemic inflammation plays an important function in the genesis and progression of atherosclerosis [35]. Furthermore, increasing hs-CRP levels are associated with the extension of infarct and with increased possibility of cardiac rupture [36]. Previous studies showed that vitamin D intake might reduce inflammatory factors by inhibiting the production of IL-6 [37, 38]. Moreover, vitamin D may inhibit the nuclear factor κB (NF-κB) activity by increasing the expression of IκB, which in turn would result in a significant decrease in the production of pro-inflammatory factors, such as IL-8 [39].

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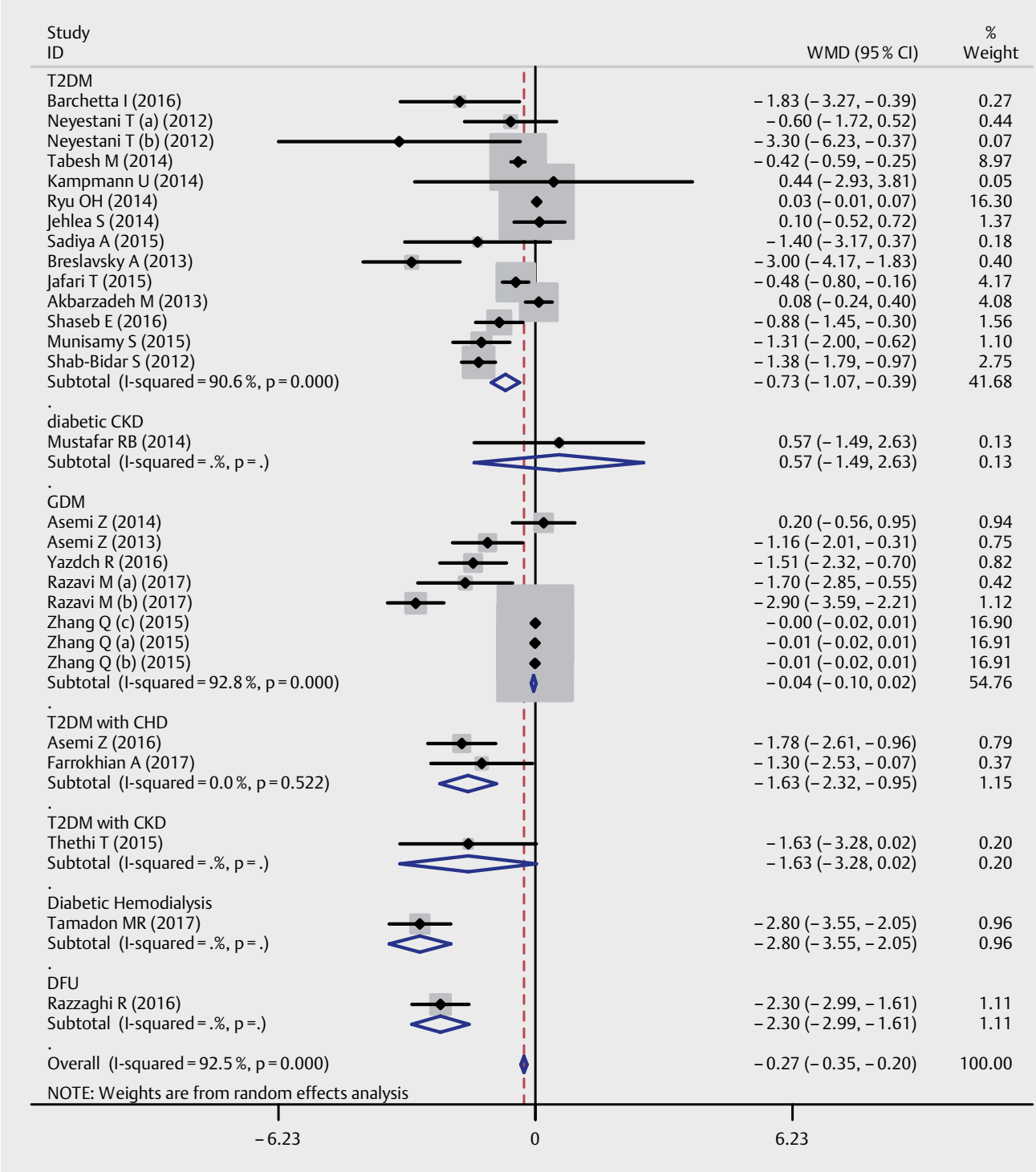

▶ **Fig. 3** Forest plot of the mean difference for the effects of vitamin D supplementation on serum hs-CRP levels in diabetic patients based on the type of disease.

Our meta-analysis of RCTs showed that vitamin D supplementation resulted in a significant increase in TAC and GSH, and a significant decrease in MDA levels in diabetics. Data on the effects of vitamin D supplementation on oxidative stress biomarkers in diabetics has been inconsistent. Some studies have reported that vitamin D was useful in improving few biomarker of oxidative stress [15, 40], while others did not observe such beneficial effects in diabetic people [41]. Furthermore, in a cross-sectional study in people with T2DM, circulating levels of serum 25-hydroxyvitamin D were inversely related to some circulating oxidative stress biomarkers such as advanced oxidation protein products [42]. Other studies have documented that vitamin D levels were inversely correlated

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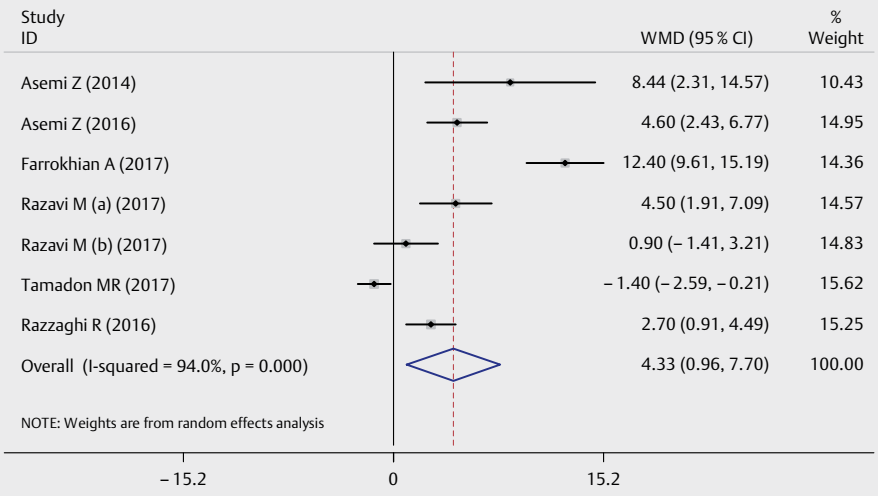
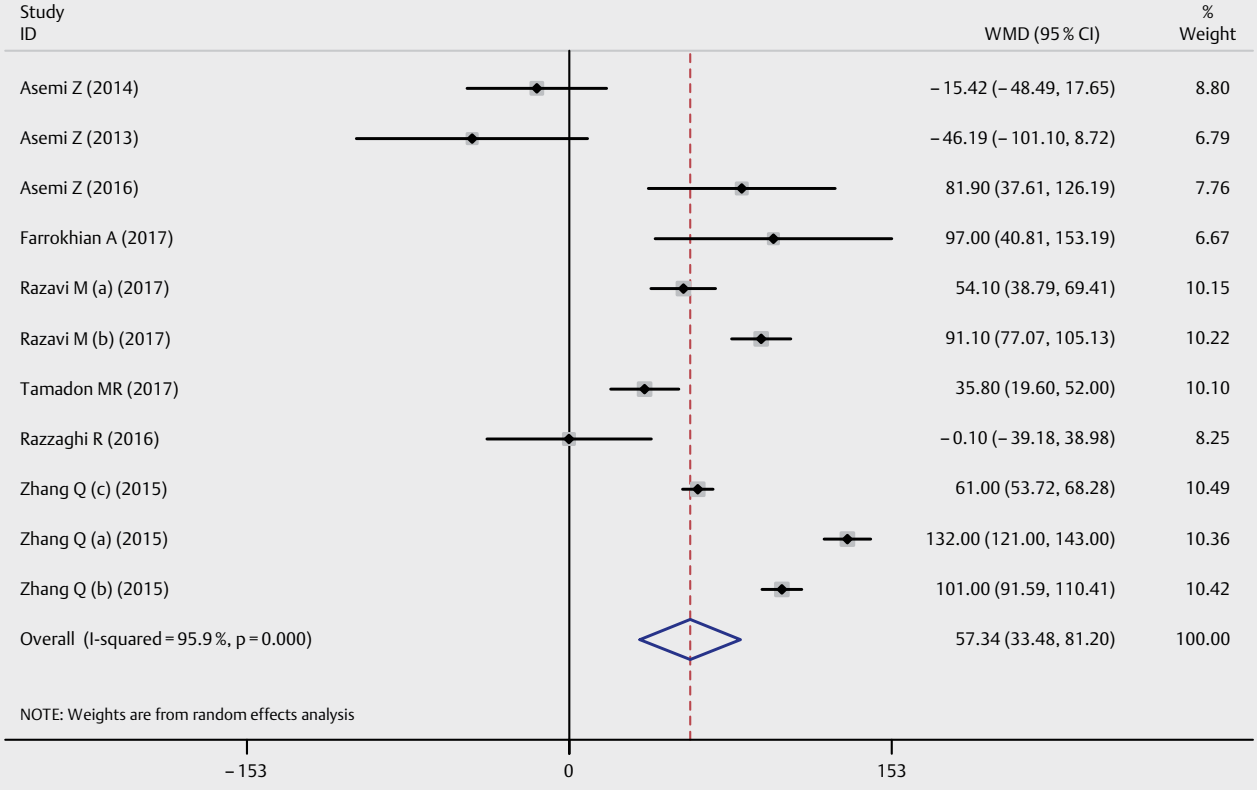


▶ **Fig. 4** Forest plot of the mean difference for the effects of vitamin D supplementation on NO levels among diabetic patients.



▶ **Fig. 5** Forest plot of the mean difference for the effects of vitamin D supplementation on TAC levels among diabetic patients.

with other markers of oxidative stress, such as urinary isoprostanes and serum lipid peroxides [12, 43]. A large number of clinical studies have demonstrated that diabetic people are susceptible to increased oxidative stress through the enhanced production of lipids, proteins and DNA oxidation products [44, 45]. In addition, oxidative stress biomarkers have been related to the pathogenesis of diabetes-related vascular complications [46]. The decreasing markers of free radical damage of lipids and proteins, and pro-inflammatory factors by vitamin D may explain its antioxidant effects [47]. In addition, the antioxidant properties of vitamin D is attributed to

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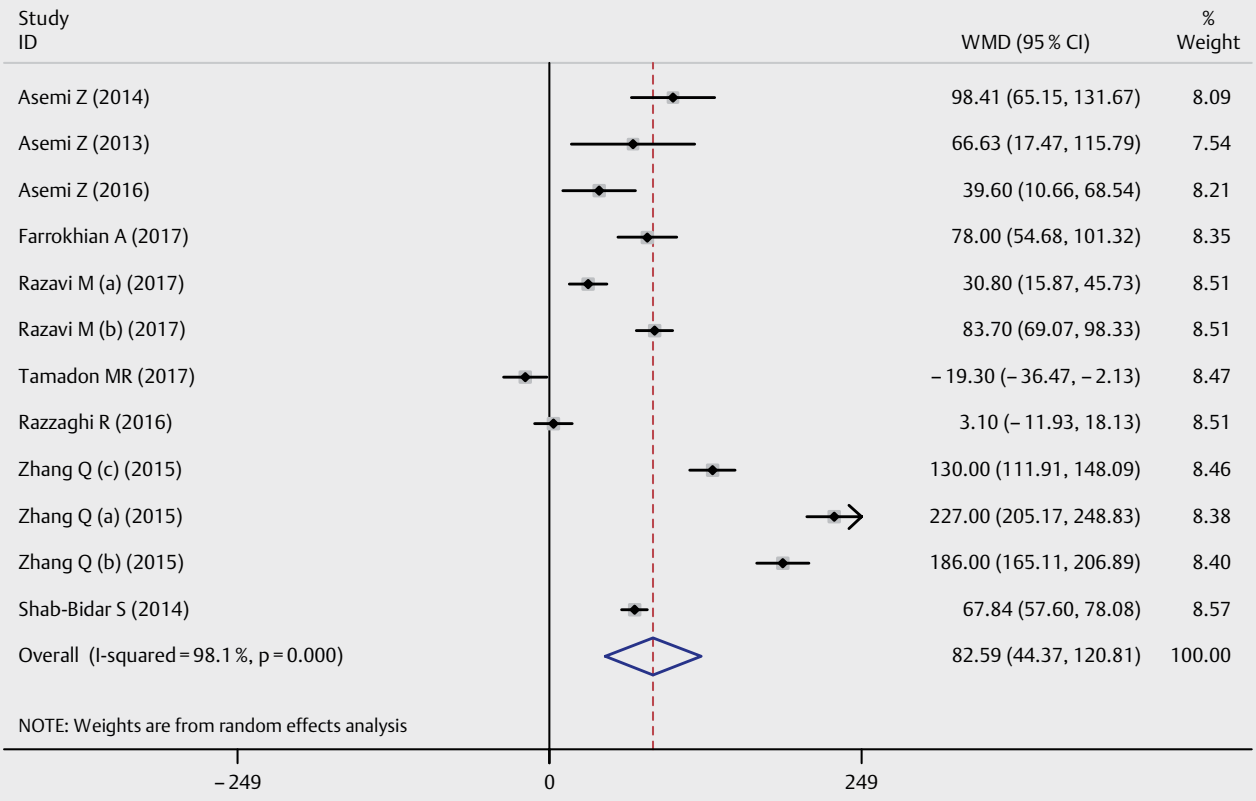
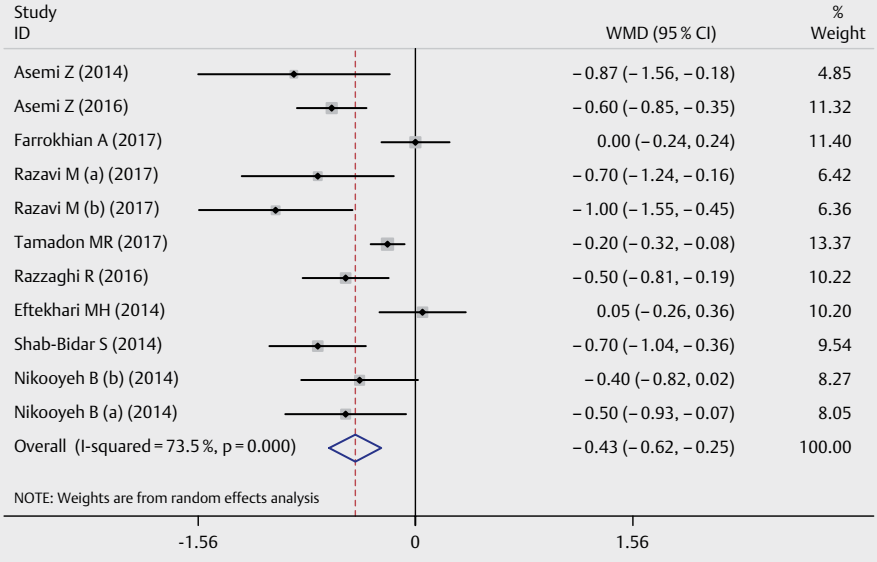


▶ **Fig. 6** Forest plot of the mean difference for the effects of vitamin D supplementation on GSH levels among diabetic patients.



▶ **Fig. 7** Forest plot of the mean difference for the effects of vitamin D supplementation on MDA levels among diabetic patients.

decreased lipid peroxidation, suppressed gene expression of nicotinamide adenine dinucleotide phosphate enzyme and inhibiting accumulation of the advanced glycation end products [12, 48].

The current study has a few limitations. Various doses of vitamin D were administered for intervention in the included studies. We were unable to assess the dose response association between supplementation and biomarkers of inflammation and oxidative.

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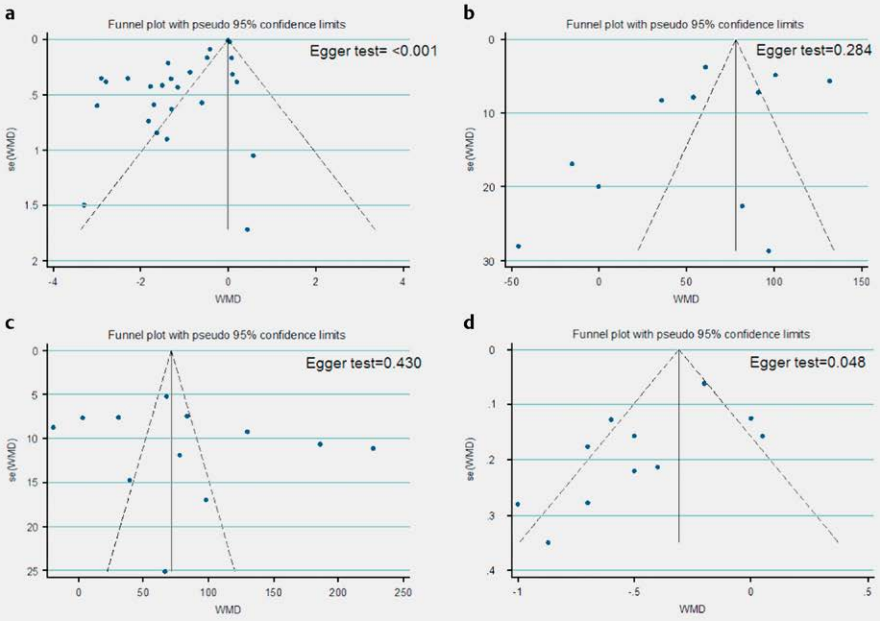

▶ **Fig. 8** Funnel plot of included studies for **a** hs-CRP, **b** TAC, **c** GSH, and **d** MDA.

One of the major limitations of the study was the inclusion of studies with relatively small sample size that could influence type-2 statistical error. Another limitation of this study was an evidence of publication bias regarding the effect of vitamin D on the hs-CRP levels. So the results should be interpreted with more caution.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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