DSX 17 (2023) 102824

Contents lists available at ScienceDirect

Diabetes & Metabolic Syndrome: Clinical Research & Reviews

journal homepage: www.elsevier.com/locate/dsx

The effects of vitamin C supplementation on glycemic control in patients with type 2 diabetes: A systematic review and meta-analysis

Saeed Nosratabadi [a], Damoon Ashtary-Larky [b], Fatemeh Hosseini [c], Zahra Namkhah [d], Shooka Mohammadi [e], Shekoufeh Salamat [f], Maryam Nadery [g], Sazin Yarmand [h], Mohammad Zamani [i,**], Alexei Wong [j], Omid Asbaghi [k,l,*]

[a] Department of Nutrition, Electronic Health and Statistics Surveillance Research Center, Science and Research Branch, Islamic Azad University, Tehran, Iran
[b] Nutrition and Metabolic Diseases Research Center, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran
[c] Department of Clinical Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Science, Tehran, Iran
[d] Department of Nutrition, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
[e] Department of Social and Preventive Medicine, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia
[f] Department of Nutrition, Faculty of Allied Medical Sciences, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran
[g] Department of Dietetics and Nutrition, Robert Stempel College of Public Health & Social Work, Florida International University, Miami, Florida, USA
[h] School of Nutrition and Food Sciences, Shiraz University of Medical Sciences, Shiraz, Iran
[i] Department of Clinical Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences, Tehran, Iran
[j] Department of Health and Human Performance, Marymount University, Arlington, Virginia, USA
[k] Cancer Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[l] Student Research Committee, Shahid Beheshti University of Medical Sciences, Tehran, Iran

ARTICLE INFO

Keywords:
Glycemic profile
Hyperglycemia
Diabetes
Vitamin C
Meta-analysis
Systematic review

ABSTRACT

Background and aim: It has been suggested that taking vitamin C supplements may improve glycemic control in patients with type 2 diabetes mellitus (T2DM). However, there has not been a thorough evaluation of the actual impact or certainty of the findings. This systematic review and meta-analysis was conducted to determine the effect of vitamin C supplementation on glycemic profile in T2DM patients.

Methods: A systematic search was performed across online databases including Scopus, Web of Science, and PubMed/Medline to identify relevant randomized controlled trials (RCTs) published until July 2022. A random-effects model was applied for the meta-analysis.

Results: The present meta-analysis included a total of 22 RCTs with 1447 patients diagnosed with T2DM.A pooled analysis revealed a significant decrease in levels of serum hemoglobin A1c (HbA1c), fasting insulin, and fasting blood glucose (FBG) in vitamin C-treated T2DM patients compared with their untreated counterparts. The dose-response evaluation displayed a substantial linear association between the intervention duration and changes in serum HbA1c levels. However, the analysis did not demonstrate any significant effect of vitamin C on serum values of homeostasis model assessment of insulin resistance(HOMA-IR) in diabetic patients. Subgroup analyses indicated that high-dose vitamin C administration (≥1000 mg/d) considerably decreased serum HOMA-IR levels.

Conclusion: These findings suggest that long-term (≥12 weeks) and high-dose vitamin C supplementation (≥1000 mg/d) may ameliorate glycemic profile in T2DM patients. However, additional high-quality RCTs are necessary to validate these results.

* Corresponding author. Cancer Research Center, Shahid Beheshti University of Medical sciences, Tehran, Iran.
** Corresponding author.
E-mail addresses: saeednosratabadi1995@gmail.com (S. Nosratabadi), Damoon_ashtary@yahoo.com (D. Ashtary-Larky), Sfatemehosseini95@gmail.com (F. Hosseini), namkhah.zahra@gmail.com (Z. Namkhah), shooka.mohammadi@gmail.com (S. Mohammadi), shekooofeh@yahoo.com (S. Salamat), mnade017@fiu.edu (M. Nadery), yarmandsazin@yahoo.com (S. Yarmand), md_zamany@yahoo.com (M. Zamani), awong@marymount.edu (A. Wong), omid.asbaghi@gmail.com (O. Asbaghi).

https://doi.org/10.1016/j.dsx.2023.102824
Received 6 August 2022; Received in revised form 21 June 2023; Accepted 26 June 2023
Available online 7 July 2023

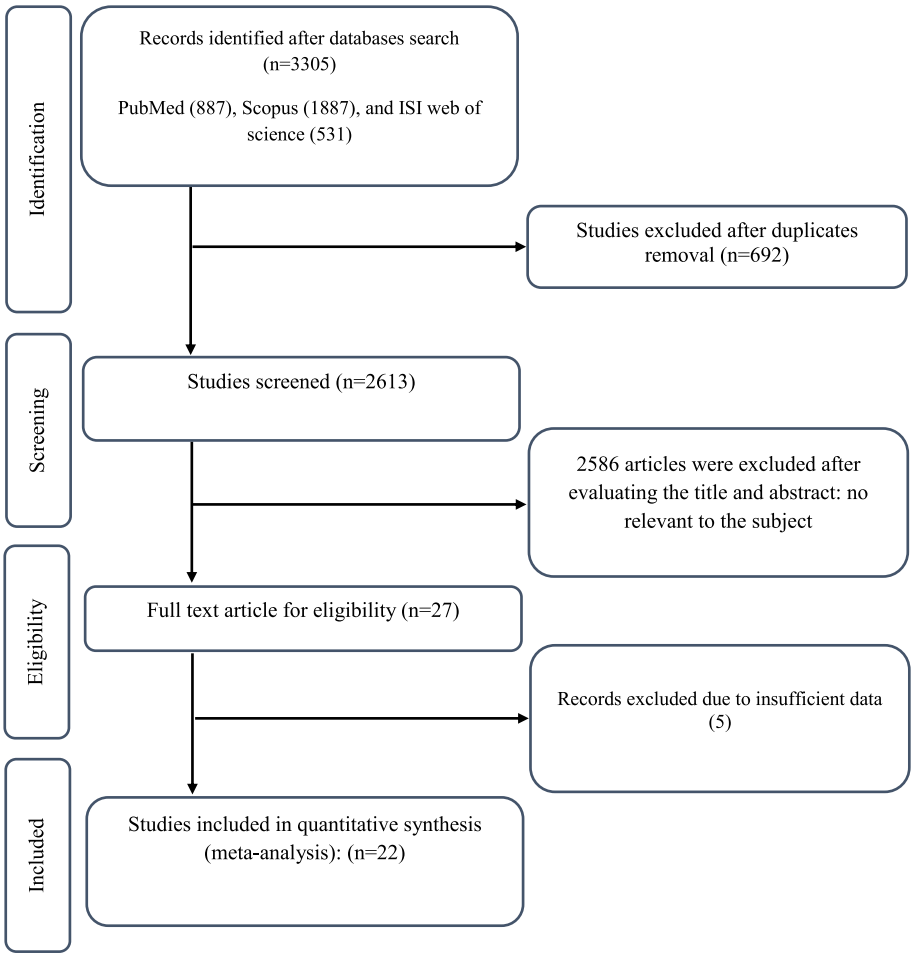


Fig. 1. Flowchart of study selection.

1. Introduction

Type 2 diabetes mellitus (T2DM) is a chronic condition that results from insufficient insulin secretion or insulin resistance [1]. Diabetes affects almost half a billion people globally, and this number is expected to reach 700 million by 2045 [2]. The prevalence of abnormal glucose tolerance in the adult population is projected to be 8.0% in 2030, increasing to 8.6% by 2045 [3]. Poor glycemic control can lead to complications such as retinopathy, neuropathy, and nephropathy [4]. Physical activity (PA), diet, and dietary supplements have been proposed as potential ways to improve T2DM complications [5–9]. In addition, there is evidence to suggest that oxidative stress and chronic low-grade inflammation may contribute to the progression, complications, and onset of T2DM. Therefore, consuming a healthy diet rich in antioxidants may be beneficial in reducing the risk of T2DM [10,11].

Consuming an optimal amount of antioxidants may lower the risk of developing T2DM and diabetic complications [10]. Antioxidant vitamin supplements can help to normalize levels of lipid peroxidation and cellular markers of oxidative stress [12]. Ascorbic acid (AA), which is a major component of vitamin C, has antioxidant properties [13]. It can be obtained from fruits and vegetables or taken as a dietary supplement [14]. Previous research has shown a negative relationship between vitamin C levels and the risk of T2DM [15,16]. Oxidative reactions may contribute to the progression of T2DM by causing insulin resistance and impeding insulin secretion [17]. The antioxidant capacity of vitamin C can help to reduce oxidative stress and lower the risk of T2DM [18].

The impacts of supplementation with vitamin C on glycemic profile in T2DM patients and the certainty of evidence were equivocal in previous studies [19–22]. Some studies have reported that taking vitamin C supplements can significantly reduce the levels of hemoglobin A1c (HbA1c) and fasting blood glucose (FBG) in the blood [19,20]. However, another study found no significant impact of vitamin C supplements on HbA1c, FBG, or insulin levels [21].

Although vitamin C supplementation plays an essential role in treating diabetes, its effects on patients with T2DM have not been thoroughly examined. While a recent meta-analysis evaluated the effectiveness of vitamin C supplementation to improve glycemic control in T2DM patients [23], it did not include several randomized controlled trials (RCTs) [24–26]. Therefore, a new systematic review and meta-analysis were conducted to investigate the impact of vitamin C supplementation on the glycemic profile of patients with T2DM.

2. Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) framework was utilized in conducting this systematic review and meta-analysis [27]. The protocol of the study was registered in the international prospective register of systematic reviews (PROSPERO) (registration number: CRD42021289736).

2.1. Search strategy

A single reviewer conducted a comprehensive search of Scopus, PubMed/Medline, and Web of Science databases to identify relevant randomized controlled trials (RCTs) published until July 2022. Two separate reviewers (ZN and FH) evaluated the articles and selected

Table 1
Characteristics of included studies in the meta-analysis.

Study	country	Study design	Sex	Study duration (weeks)	Sample size (interventions/controls)		Participant's age (years)		Participant's BMI (kg/m^2)		Intervention	
					IG	CG	IG	CG	IG	CG	IG	CG
Paolisso et al., 1995 [10]	Italy	Cross-over	M/F (19/21)	16	40	40	72 ± 0.5	72 ± 0.5	27.7 ± 0.3	27.7 ± 0.3	Vitamin C 500 mg (2/day)	Placebo
Evans et al., 2003 [24]	United Kingdom	Parallel	M/F (17/3)	6	10	10	52.7 ± 6.9	53.6 ± 7.9	29·2	28·6	Vitamin C 1000 mg (1/day)	Placebo-insulin
Lu et al., 2005 [22]	Sweden	Cross-over	M/F (12/5)	2	17	17	54.00	54.00	NR	NR	Vitamin C 1000 mg (3/day)	Placebo
Chen et al., 2006 [36]	USA	Parallel	M/F (13/19)	4	15	17	49 ± 7.7	47 ± 12.3	34.00	36.00	Vitamin C 800 mg (1/day)	Placebo
Tousoulis et al., 2007 [37]	Greece	Parallel	M/F (14/12)	4	13	13	59.1 ± 8.65	60.9 ± 11.17	29.10	28.00	Vitamin C 2000 mg (1/day)	No treatment
Dakhale et al., 2011 [38]	India	Parallel	M/F (28/38)	12	33	33	48.33 ± 7.9	45.88 ± 8.1	NR	NR	Vitamin C 500 mg (2/day)	Placebo-metformin
Shakouri-Mahmoudabadi et al., 2011(A) [20]	Iran	Parallel	M (34)	8	17	17	52.6 ± 5.4	50.3 ± 8.9	29.30	28.90	Vitamin C 200 mg (1/day)	Placebo
Shakouri-Mahmoudabadi et al., 2011(B) [20]	Iran	Parallel	M (31)	8	15	16	52.1 ± 6.3	54.2 ± 4.8	29.3 ± 4.2	30.4 ± 3.4	EPA 500 mg (1/day) + vitamin C 200 mg (1/day)	EPA 500 mg (1/day) + placebo
Rafighi et al., 2011 (A) [39]	Iran	Parallel	M/F (40/39)	12	39	40	54.40 ± 4.74	51.09 ± 7.83	30.43 ± 3.91	29.29 ± 3.17	Vitamin C 266.7 mg (3/day)	Placebo
Rafighi et al., 2011 (B) [39]	Iran	Parallel	M/F (44/42)	12	43	43	51.26 ± 5.83	52.47 ± 5.53	33.17 ± 3.32	30.86 ± 3.76	Vitamin C 266.7 mg (3/day), vitamin E 300 IU (3/day)	Vitamin E 300 IU (3/day)
Bhatt et al., 2012 [40]	India	Parallel	M/F (17/44)	12	30	29	57.53 ± 7.44	63.17 ± 9.07	25.82	24.92	Vitamin C 500 mg (1/day)	No treatment
Siavash et al., 2014 [41]	Iran	Parallel	M/F (12/18)	6	15	15	53.47 ± 9.95	52.53 ± 8.97	26.7 ± 4.8	28.0 ± 3.6	Vitamin C 1000 mg (1/day), gemfibrozil 600 mg (1/day)	Gemfibrozil (600 mg)
Ghaffari et al., 2015 [42]	Iran	Parallel	M/F (13/17)	8	17	14	51.9 ± 5.92	51.9 ± 5.92	NR	NR	Vitamin C 800 mg (1/day)	Placebo
Nayaka et al., 2015 (A) [26]	India	Parallel	M/F (60)	8	28	14	48	47.26	26.7	26.8	Vitamin C 500 mg (2/day), glibenclamide 5 mg (2/d)	Glibenclamide 5 mg (2/d)
Nayaka et al., 2015 (B) [26]	India	Parallel	M/F (60)	8	27	14	48.33	47.26	26.7	26.8	vitamin C 500 mg (4/day), glibenclamide 5 mg (2/d)	Glibenclamide 5 mg (2/d)
Mason et al., 2016 [43]	Australia	Cross-over	M/F (12/2)	16	14	14	59.4 ± 3.5	59.4 ± 3.5	30.60	30.70	Vitamin C 500 mg (2/day)	Placebo
Sanguanwong et al., 2016 [44]	Thailand	Parallel	M/F (100)	8	50	50	57.50	58.00	25.40	25.60	Vitamin C 1000 mg (1/day)	Placebo
Hamed et al., 2016 [25]	Palestine	Parallel	M/F (20/19)	12	19	20	36–60	40–60	27–31	27–32	Vitamin C 500 mg (2/day)	No treatment
Gillani et al., 2017 [45]	Malaysia	Parallel	M/F (281)	48	139	142	38.12 ± 8.16	37.93 ± 7.89	23.50	24.30	Vitamin C 500 mg (1/day)	Placebo-metformin
El-Aal et al., 2018 (A) [46]	Palestine	Parallel	M (20)	12	10	10	51.02	51.02	33.86	29.43	Vitamin C and metformin 500 mg (2/day)	Placebo-metformin 500 mg (2/day)
El-Aal et al., 2018 (B) [46]	Palestine	Parallel	M (20)	12	10	10	51.02	51.02	30.74	29.82	Metformin500mg (2/day), vitamin C 500 mg (2/day), vitamin E 400 mg (2/day)	Metformin500mg (2/day), vitamin E 400 mg (2/day)
Froghi et al., 2018 [47]	Iran	Parallel	M/F (37/41)	8	38	40	56/87 ± 6/59	56/48 ± 5/46	27/56	27/47	250 mg (2/day)	Placebo
Mason et al., 2018 [21]	Australia	Parallel	M/F (26/5)	16	31	31	61.8 ± 6.8	61.8 ± 6.8	29.1 ± 3.1	29.1 ± 3.1	500 mg (2/day)	Placebo

(*continued on next page*)

Table 1 (*continued*)

Study	country	Study design	Sex	Study duration (weeks)	Sample size (interventions/controls)		Participant's age (years)		Participant's BMI (kg/m^2)		Intervention	
					IG	CG	IG	CG	IG	CG	IG	CG
Kunsongkeit et al., 2019 [48]	Thailand	Parallel	M/F (9/22)	8	15	16	59.87 ± 11.3	57.94 ± 14.0	NR	NR	500 mg (1/day)	Placebo
Ragheb et al., 2020 [50]	Egypt	Parallel	M/F (10/23)	8	20	13	55.95 ± 7.49	57.15 ± 8.41	34.40	32.31	500 mg (1/day)	No treatment
Devanandan et al., 2020 [49]	India	Parallel	M/F (84/51)	36	68	67	48.2 ± 7.2	41.6 ± 8.2	23.20	24.30	500 mg (1/day)	Placebo-metformin

Abbreviations: IG, intervention group; CG, control group; NR, not reported; F, female; M, male; NR, not reported; EPA, eicosapentaenoic acid.

Table 2
Quality assessment.

Study	Random sequence generation	Allocation concealment	Selective reporting	Other sources of bias	Blinding (participants and personnel)	Blinding (outcome assessment)	Incomplete outcome data	General quality
Paolisso et al., 1995 [10]	L	L	L	U	L	U	L	Good
Evans et al., 2003 [24]	H	U	L	H	H	H	L	Weak
Lu et al., 2005 [22]	L	L	U	L	U	U	L	Good
Chen et al., 2006 [36]	U	L	L	H	L	H	L	Fair
Tousoulis et al., 2007 [37]	U	H	L	U	H	H	L	Weak
Dakhale et al., 2011 [38]	L	L	H	U	L	H	L	Weak
Shakouri-Mahmoudabadi et al., 2011 [20]	U	U	L	U	L	U	L	Good
Rafighi et al., 2011 [39]	H	H	L	L	H	U	L	Weak
Bhatt et al., 2012 [40]	H	U	L	L	L	L	L	Fair
Siavash et al., 2014 [41]	L	L	U	H	H	H	L	Weak
Ghaffari et al., 2015 [42]	H	L	L	H	L	L	L	Fair
Nayaka et al., 2015 [26]	H	U	L	U	L	L	L	Good
Mason et al., 2016 [43]	L	L	U	L	L	U	L	Good
Sanguanwong et al., 2016 [44]	L	L	U	U	L	U	L	Good
Hamed et al., 2016 [25]	H	U	H	H	H	U	L	Weak
Gillani et al., 2017 [45]	L	L	U	U	H	H	L	Fair
El-Aal et al., 2018 [46]	U	H	L	H	H	H	L	Weak
Froghi et al., 2018 [47]	L	L	L	U	L	U	L	Good
Mason et al., 2018 [21]	L	L	L	U	L	U	L	Good
Kunsongkeit et al., 2019 [48]	L	L	U	H	L	U	H	Fair
Ragheb et al., 2020 [50]	L	H	H	H	H	H	L	Weak
Devanandan et al., 2020 [49]	L	U	H	H	U	U	L	Fair

Abbreviations: L, low risk of bias; H, high-risk of bias; U, unclear risk of bias.
General quality: Good<2 high-risk of bias; Fair = 2 high-risk of bias, Weak> 2 high-risk of bias.

eligible RCTs based on the established inclusion criteria. The following medical subject headings (MeSH) and non-MESH were selected in the search strategy: ((“ascorbic acid” OR “vitamin C” OR “ascorbate”) AND (“T2DM” OR “Type 2 diabetes” OR “diabetes”) AND (“controlled trial” OR “intervention” OR “random” OR “randomly” OR “clinical trial” OR “placebo” OR “randomized controlled trial” OR “trial” OR “randomized clinical trial” OR “blinded” OR “RCT” OR “double-blinded” OR “double-blind” OR “Cross-Over” OR “parallel”).

2.2. Study selection criteria

The EndNote reference management software was used to import the identified references. Two reviewers (ZN and FH) independently screened the titles and abstracts of the articles. Any discrepancies were resolved through discussion or with the help of a third investigator (OA). This systematic review and meta-analysis included all RCTs (with parallel or crossover design) that investigated the impact of vitamin C supplementation on the levels of FBG, HbA1c, homeostasis model assessment of insulin resistance(HOMA-IR), and fasting insulin in T2DM patients who received vitamin C treatment compared to those who did not.

Included RCTs in this review involved adult patients diagnosed with T2DM and had a parallel or cross-over design with a control or placebo group. They lasted for more than 2 weeks and had pre-post measurements of the selected outcomes in both groups at the endpoint and baseline. The study focused on assessing the effects of vitamin C supplementation on glycemic indices in T2DM patients and did not consider vitamin C as part of a multi-component supplement in the intervention or control group. RCTs that did not meet these criteria, such as uncontrolled or non-placebo-controlled studies, studies with participants below 18 years of age, studies lasting less than 2 weeks, non-RCTs or observational studies, and studies that had insufficient data on the selected outcomes at baseline or follow-up measurements, were excluded.

Table 3
GRADE profile of vitamin C supplementation for FBG, fasting insulin, HbA1c, and HOMA-IR scores in the T2DM patients.

Quality assessment						Summary of findings		Quality of evidence
Outcomes	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Number of intervention/control	WMD (95%CI)	
FBG	No serious limitations	Very serious[a]	No serious limitations	No serious limitations	No serious limitations	736/736	−10.67 (−18.46, −2.89)	⊕⊕◯◯ Low
Fasting insulin	No serious limitations	Very serious[b]	No serious limitations	No serious limitations	No serious limitations	259/253	−1.74 (−3.16, −0.33)	⊕⊕◯◯ Low
HbA1c	No serious limitations	Very serious[c]	No serious limitations	No serious limitations	No serious limitations	623/624	−0.51 (−0.81, −0.20)	⊕⊕◯◯ Low
HOMA-IR	No serious limitations	Very serious[d]	No serious limitations	Serious Limitations[e]	No serious limitations	143/140	−0.85 (−2.04, 0.33)	⊕◯◯◯ Very low

Abbreviations: FBG, fasting blood glucose; HbA1c, hemoglobin A1c; HOMA-IR, homeostasis model assessment for iInsulin resistance.
[a] The test for heterogeneity is significant, and the I^2 is moderate, 85.6%.
[b] The test for heterogeneity is significant, and the I^2 is moderate, 82.6%.
[c] The test for heterogeneity is significant, and the I^2 is moderate, 89.6%.
[d] The test for heterogeneity is significant, and the I^2 is moderate, 86.9%.
[e] Values are distributed in opposite directions across studies.

2.3. Data extraction

The necessary information was extracted by two independent researchers (ZN and FH) from eligible full-text articles. They discussed any differences and came to a consensus. They gathered data on various aspects of the studies, such as the publication year, sample size, study design, first author's name, trial duration and location, and dose of vitamin C supplement. Additionally, they collected demographic information about the participants, such as mean age, BMI, and gender. Pre- and post-measurements of selected outcomes at baseline and endpoints of the study were also collected. The primary outcomes were serum levels of FBG, fasting insulin, HOMA-IR, and HbA1c.

2.4. Risk of bias assessment

Two independent investigators (ZN and FH) appraised the quality of RCTs based on the Cochrane risk of bias (RoB) tool [28]. It identified probable sources of bias comprising blinding of participants and outcome evaluation, allocation concealment, selective reporting, random sequence generation, incomplete outcome data, and other sources of bias. Unclear, high, and low risk of bias scores were considered for each domain [28].

2.5. Certainty assessment

The quality of evidence was evaluated using the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) guideline, which classifies it into categories such as high, moderate, low, or very low [29].

2.6. Statistical analysis

The meta-analysis was conducted using Stata software (version 14). The changes in glycemic indices due to vitamin C supplementation were analyzed using weighted mean differences (WMDs) and 95% confidence intervals (CIs) to determine the effect size. Mean and standard deviation (SD) were used to report the outcome measures. The effect size was calculated as the mean difference between the interventional and control groups at baseline and endpoints. In addition, the subsequent formula was employed to compute SD changes from baseline to the endpoints: $\sqrt{\text{SD [2]}_{\text{baseline}} + \text{SD [2]}_{\text{final}} - (2 \times R \times \text{SD}_{\text{baseline}} \times \text{SD}_{\text{final}})}$ [30]. Pooled WMDs were computed using the random-effects model [31]. Heterogeneity between trials was assessed using the I^2 statistic [32]; I^2 values of 75%, 25%, and 50% were allocated as high, low, and medium heterogeneity, respectively [33].

Sub-group analyses were performed to identify potential reasons for differences between the studies. They analyzed the data based on the dosage of vitamin C administered (<1000 mg/day vs. ≥1000 mg/day) and the length of the trials (<12 weeks vs. ≥12 weeks). Leave-one-out sensitivity analyses were carried out to identify the impact of each trial on the overall analysis. Furthermore, funnel plots, Begg's and Egger's tests were used to detect any potential publication bias [34]. A p-value <0.05 was used to determine statistical significance. A fractional polynomial model wasapplied to detect any potential non-linear relationship between vitamin C dosage (mg/day) and trial duration (weeks). Furthermore, they employed meta-regression to assess any linear correlation between vitamin C dosage, intervention duration, and effect size [35].

3. Results

3.1. Study selection

A primary multi-database search identified 3305 records. After removing duplicates (n = 692), 2613 records were screened and 2586 reports were omitted. The full texts of *27 articles were evaluated and 22 eligible RCTs* [10,20–22,24–26,36–50] *were identified for this meta-analysis* (Fig. 1).

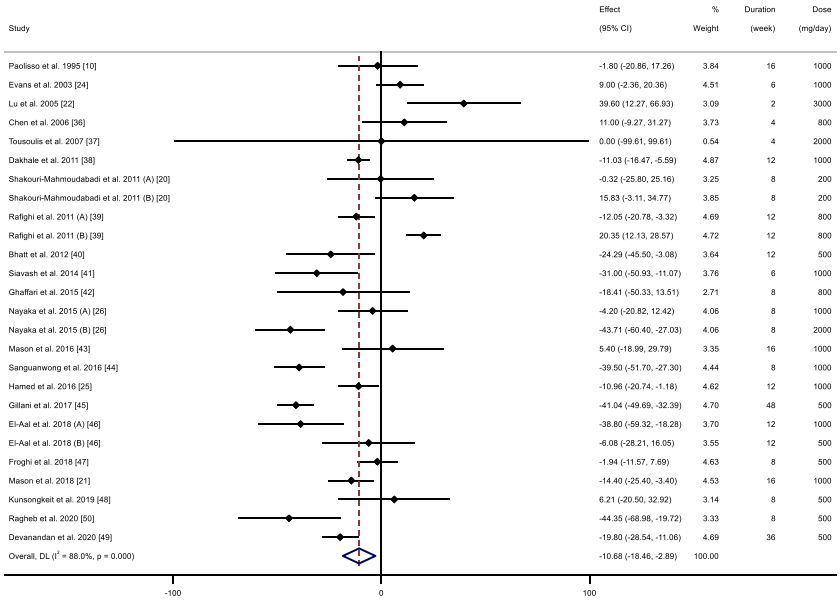
3.2. Study characteristics

The current systematic review and meta-analysis included 22 RCTs that enrolled 1447 T2DM patients. The characteristics of the trials were summarized in Table 1. Nineteen trials had a parallel design, while three were cross-over studies [10,22,43]. The articles were published between 1995 and 2020. These trials were carried out in the United States (US) [36], Iran [20,39,41,42,47], the United Kingdom (UK) [24], Italy [10], Sweden [36], Australia [21,43], Greece [37], India [26,38,40,49], Thailand [44,48], Malaysia [45], Palestine [25,46], and Egypt [50]. The length of interventions and sample sizes ranged from 2 to 48 weeks and 7 to 139 diabetic patients, respectively. The mean age and body mass index (BMI) of the participants ranged from 36 to 72 years and 25.4–34.4 kg/m^2, respectively. The majority of RCTs (n = 20) were performed among both sexes, while two studies included only men [46,51]. A daily dose of vitamin C was between 250 and 2000 mg.

3.3. Risk of bias assessment

Risk of bias evaluation was provided for 22 eligible RCTs in Table 2. Eight studies had good quality in all domains of bias [10,20,21,26,43,44,47,52]. The quality of six [36,40,42,45,48,49] and eight trials [24,25,37–39,41,46,50] were fair and poor, respectively.

a)



b)

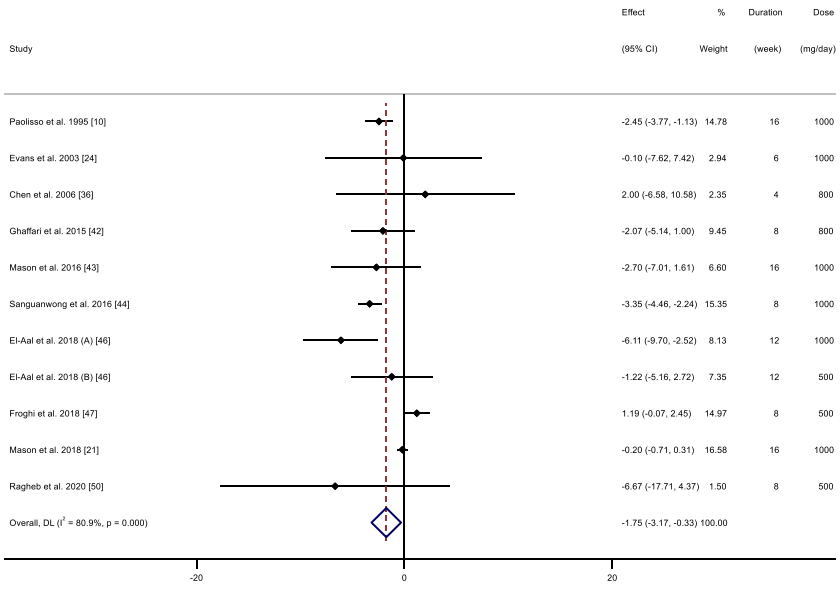
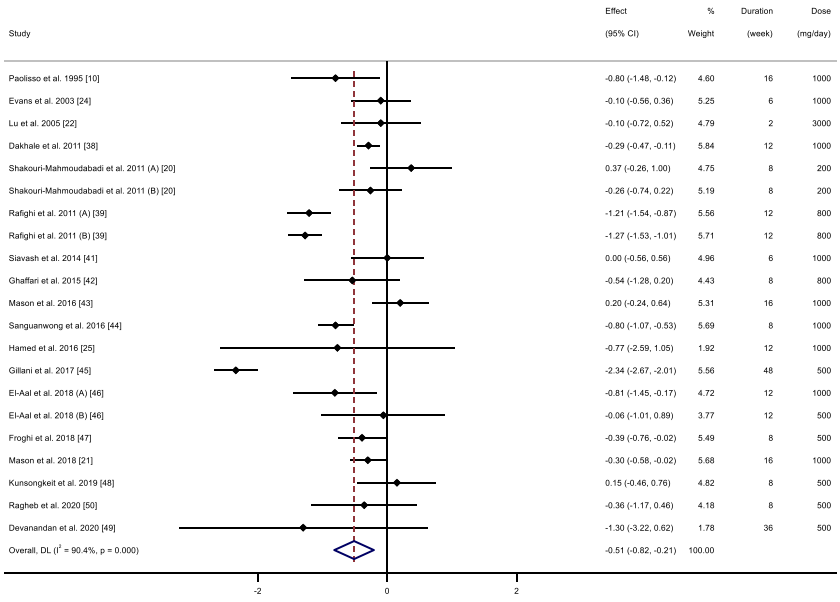


Fig. 2. Forest plot detailing weighted mean difference and 95% confidence intervals (CIs) for the effect of vitamin C supplementation on; a) fasting blood glucose (FBG), b) fasting insulin, c) hemoglobin A1c(HbA1c), and d) homeostasis model assessment for insulin resistance(HOMA-IR). Y-axis: the zero-line, x-axis: changes in a variable; the dotted red vertical line: mean difference, DL: The DerSimonian and Laird is a method to estimate the between-study variance, horizontal lines: confidence interval of each study, singular dot in the middle of horizontal lines: mean changes of each study.

c)



d)

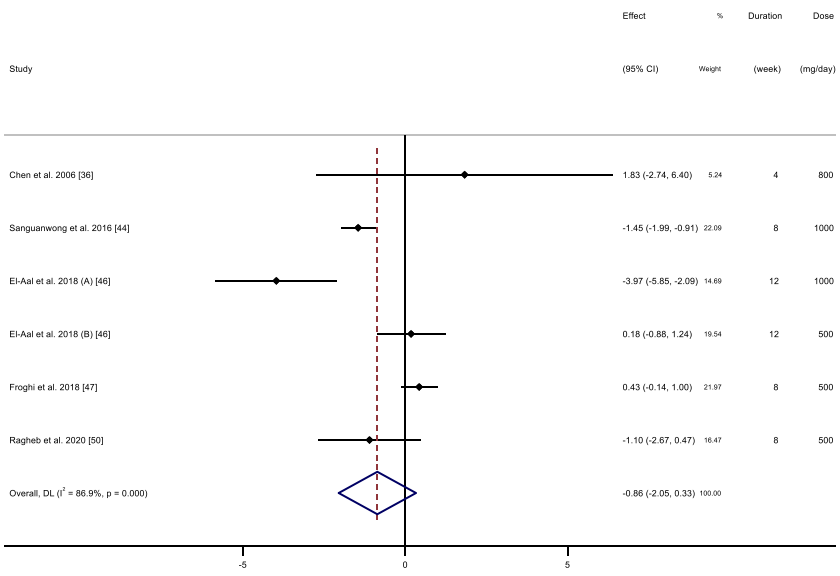


Fig. 2. (*continued*).

3.4. GRADE assessment

The certainty of evidence was determined by applying the GRADE protocol for measured outcomes (Table 3). There was a low certainty of the evidence for FBG, fasting insulin, and HbA1C outcomes due to the risk of inconsistency. HOMA-IR outcome was considered to have a very low quality of evidence and was downgraded for the serious risk of imprecision and inconsistency.

3.5. Effect of vitamin C supplementation on serum FBG

Twenty-two RCTs [10,20–22,24–26,36–50] with 1447 participants (n = 773 vitamin C group, n = 745 control group) were selected for this meta-analysis; the pooled analysis indicated that supplementation with vitamin C effectively decreased serum levels of FBG in vitamin C-treated T2DM patients compared with their untreated counterparts (WMD: 10.67 mg/dL, 95% CI: 18.46, −2.89; P = 0.007). In addition, there was substantial between-studies heterogeneity (I^2 = 88.0%, P < 0.001) (Fig. 2A). Sub-group analyses identified similar outcomes in RCTs that

Table 4
Subgroup analyses of vitamin C supplementation on glycemic control in patients with T2DM.

	Number of effect sizes	WMD (95%CI)	P within group	heterogeneity		
				P heterogeneity	I^2	P between sub-groups
Subgroup analyses of vitamin C supplementation on FBG level (mg/dL)						
Overall effect	26	−10.67 (−18.46, −2.89)	**0.007**	<0.001	88.0%	
Trial duration (week)						
<12	14	−8.15 (−21.87, 4.98)	0.224	<0.001	85.5%	0.575
≥12	12	−12.93 (−23.22, −2.63)	**0.014**	<0.001	90.6%	
Vitamin C Dose (mg/d)						
<1000	13	−8.73 (−21.42, 3.95)	0.177	<0.001	90.9%	0.074
≥1000	13	−12.86 (−22.78, −2.94)	**0.011**	<0.001	83.9%	
Subgroup analyses of vitamin C supplementation on fasting insulin level (uU/mL)						
Overall effect	11	−1.74 (−3.16, −0.33)	**0.016**	<0.001	80.9%	
Trial duration (week)						
<12	6	−1.26 (−4.08, 1.55)	0.379	<0.001	83.3%	0.604
≥12	5	−2.17 (−4.11, −0.22)	**0.029**	0.001	79.9%	
Vitamin C Dose (mg/d)						
<1000	5	−0.29 (−2.34, 1.75)	0.779	0.176	36.8%	0.123
≥1000	6	−2.49 (−4.38, −0.59)	**0.010**	<0.001	87.3%	
Subgroup analyses of vitamin C supplementation on HbA1c (%)						
Overall effect	21	−0.51 (−0.81, −0.20)	**0.001**	<0.001	90.4%	
Trial duration (week)						
<12	10	−0.23 (−0.48, 0.01)	0.064	0.009	58.8%	0.045
≥12	11	−0.82 (−1.30, −0.31)	**0.001**	<0.001	94.0%	
Vitamin C Dose (mg/d)						
<1000	11	−0.65 (−1.18, −0.13)	**0.014**	<0.001	92.2%	0.263
≥1000	10	−0.33 (−0.55, −0.11)	**0.003**	0.004	63.1%	
Subgroup analyses of vitamin C supplementation on HOMA-IR						
Overall effect	6	−0.85 (−2.04, 0.33)	0.157	<0.001	86.9%	
Trial duration (week)						
<12	4	−0.48 (−1.86, 0.89)	0.490	<0.001	87.4%	0.626
≥12	2	−1.82 (−5.88, 2.24)	0.380	<0.001	93.0%	
Vitamin C Dose (mg/d)						
<1000	4	0.18 (−0.43, 0.80)	0.566	0.297	18.6%	<0.001
≥1000	2	−2.54 (−4.99, −0.09)	**0.042**	0.011	84.4%	

Abbreviations: CI, confidence interval; FBG, fasting blood glucose; HbA1c, hemoglobin A1c; HOMA-IR, homeostasis model assessment of Iinsulin resistance; WMD, weighted mean differences; T2DM, type 2 diabetes mellitus.

used high daily doses of vitamin C (≥1000 mg) and had a longer duration (≥12 weeks) (Table 4).

3.6. Effect of vitamin C supplementation on serum fasting insulin

The impact of supplementation with vitamin C on serum fasting insulin levels was assessed in 10 RCTs [10,21,24,36,42–44,46,47,50] that involved 450 T2DM patients (259 cases and 253 controls). The pooled estimation from random-effects models revealed a significant reduction in serum fasting insulin values between the two groups (WMD: 1.74 uU/mL, 95% CI: 3.16, −0.33; P = 0.016) with significant heterogeneity between trials (I2 = 80.9%, p < 0.001) (Fig. 2B). Similar results were observed in subgroup analyses of trials with a duration ≥12 weeks and high-dose vitamin C supplementation (≥1000 mg/d) **(Table 4).**

3.7. Effect of vitamin C supplementation on serum HbA1c

The meta-analysis of 18 trials (21 arms) [10,20–22,24,25,38,39,41–50] with 1247 participants indicated a significant reduction in serum values of HbA1c in the vitamin C-treated group compared to controls (WMD: 0.51%, 95% CI: 0.81, −0.20; p = 0.001) with a high degree of between-study heterogeneity (I^2 = 90.4%, p < 0.001) (Fig. 2C). Outcomes were similar based on sub-analyses in trials with duration ≥12 weeks and vitamin C dose ≥1000 (mg/d) (Table 4).

3.8. Effect of vitamin C supplementation on serum HOMA-IR

Five trials [36,44,46,47,50] with six effect sizes and 283 participants explored the effect of vitamin C administration on serum HOMA-IR levels (intervened versus untreated group); the meta-analysis did not detect any considerable differences in serum HOMA-IR values between the two groups (WMD: 0.85, 95% CI: 2.04, 0.33; P = 0.157) (Fig. 2D). In addition, there was considerable heterogeneity between studies (I^2 = 86.9%, p < 0.001). Subgroup analysis displayed a substantial reduction in serum HOMA-IR levels in trials with the administration of high-dose vitamin C (≥1000 mg/d) (Table 4).

3.9. Publication bias

There were different degrees of asymmetry for all evaluated outcomes when the funnel plots were visually inspected (Fig. 7). No publication bias was exhibited by Begg's and Egger's tests for all outcomes (fasting insulin, HbA1c, FBG, and HOMA-IR).

3.10. Linear and non-linear dose-response relations

There was no linear (Figs. 5 and 6) and non-linear (Figs. 3 and 4) association between vitamin C dose and trial duration with changes in serum FBG, fasting insulin, and HOMA-IR based on the dose-response evaluation. However, a substantial linear relationship (P < 0.001;

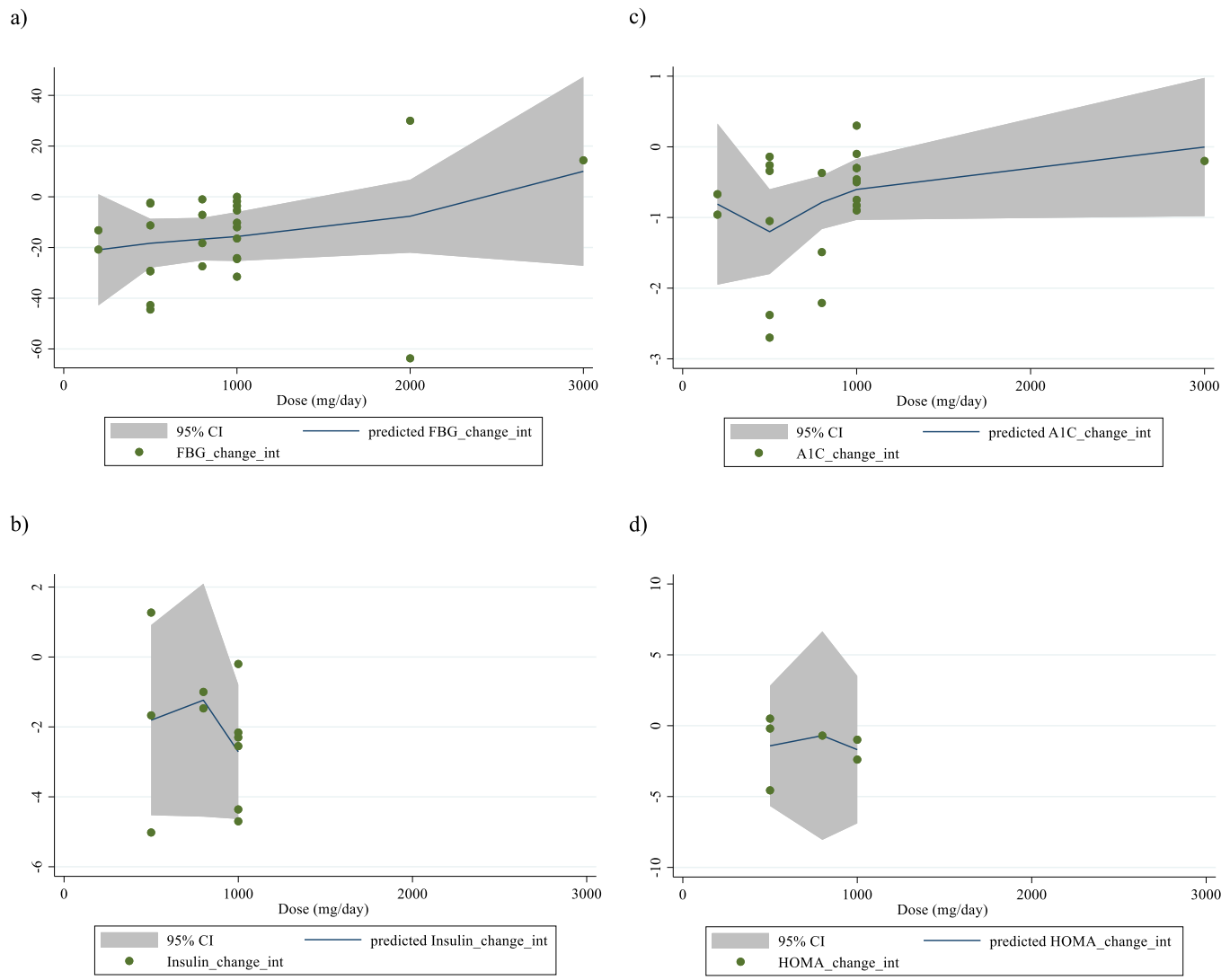


Fig. 3. Non-linear dose-response relations between daily dose (mg) of vitamin C supplementation and absolute mean differences in (a) fasting blood glucose (FBG), (b) fasting insulin, (c) hemoglobin A1c(HbA1c), and (d) homeostasis model assessment of insulin resistance (HOMA-IR). The 95% CI (confidence interval) is demonstrated in the shaded parts.

Fig. 6C) was found between intervention duration and changes in serum levels of HbA1c.

3.11. Sensitivity analysis

Sensitivity analyses depicted that the outcomes related to serum levels of FBG, HOMA-IR, and HbA1c were not influenced by removing any specific study. Meanwhile, after excluding one study [43], the results for serum fasting insulin levels were changed.

4. Discussion

This meta-analysis aimed to investigate the effects of vitamin C supplementation on glycemic profile in patients with T2DM. The results showed a significant decrease in serum levels of HbA1c, fasting insulin, and FBG in T2DM patients treated with vitamin C compared to those who were not treated. Subgroup analyses revealed similar outcomes in RCTs that administered high daily doses of vitamin C (≥1000 mg) for a longer duration (≥12 weeks). The dose-response evaluation showed a significant linear association between intervention duration and changes in serum levels of HbA1c. However, there was no significant effect of vitamin C on serum levels of HOMA-IR. Subgroup analyses indicated a significant decrease in serum HOMA-IR values in trials with high-dose vitamin C administration (≥1000 mg/d).

A recent review that examined the effects of vitamin C supplementation on glycemic control in T2DM patients found similar results to the present study, but it did not include some relevant RCTs [23]. On the other hand, a different meta-analysis that included 22 RCTs suggested that vitamin C supplementation did not improve the glycemic profile of T2DM patients [53]. However, the majority of the studies in that review did not report baseline levels of vitamin C, so the impact of preexisting vitamin C deficiency could not be determined. Additionally, the studies did not report dietary intake of vitamin C [53].

Patients with T2DM who have low serum levels of AA may benefit from vitamin C supplementation, as it may lower seum levels of FBG and fasting insulin, or improve insulin resistance [36]. Previous studies have shown that T2DM patients tend to have lower serum vitamin C levels compared to healthy individuals [54,55]. There are several possible explanations for this hypovitaminosis C in T2DM patients. One possible reason is the structural similarity between AA and glucose, which may reduce the rate of reconversion of intracellular DHA to ascorbate during hyperglycemic conditions, possibly due to increased oxidative stress [17]. Additionally, the excessive formation of free radicals related to hyperglycemia can further diminish the antioxidant capacity of vitamin

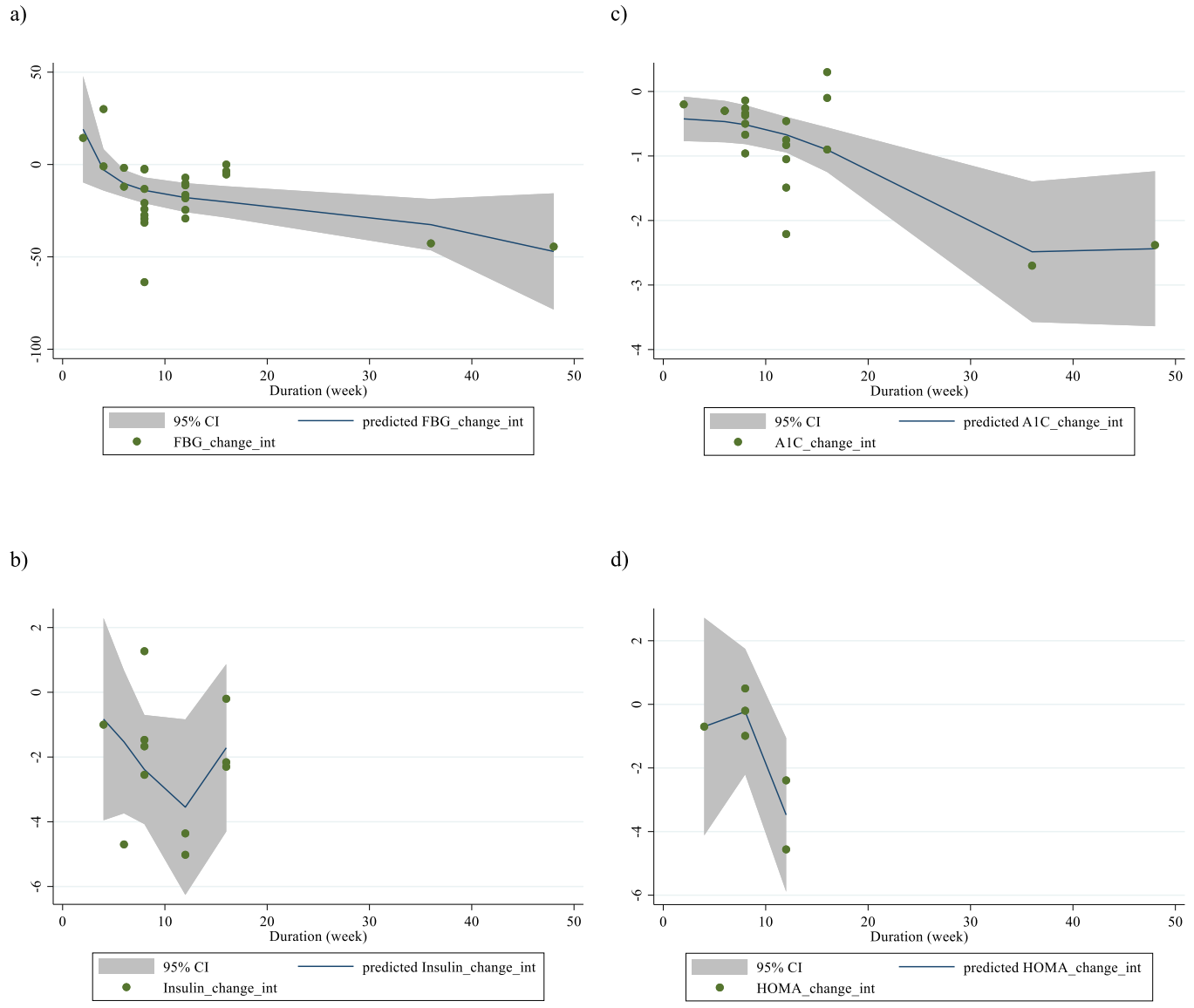


Fig. 4. Non-linear dose-response relations between intervention duration (weeks) of vitamin C supplementation and absolute mean differences in (a) fasting blood glucose (FBG),(b) fasting insulin,**(c)** hemoglobin A1c(HbA1c), and **(d)** homeostasis model assessment of insulin resistance (HOMA-IR). The 95% CI (confidence interval) is demonstrated in the shaded parts.

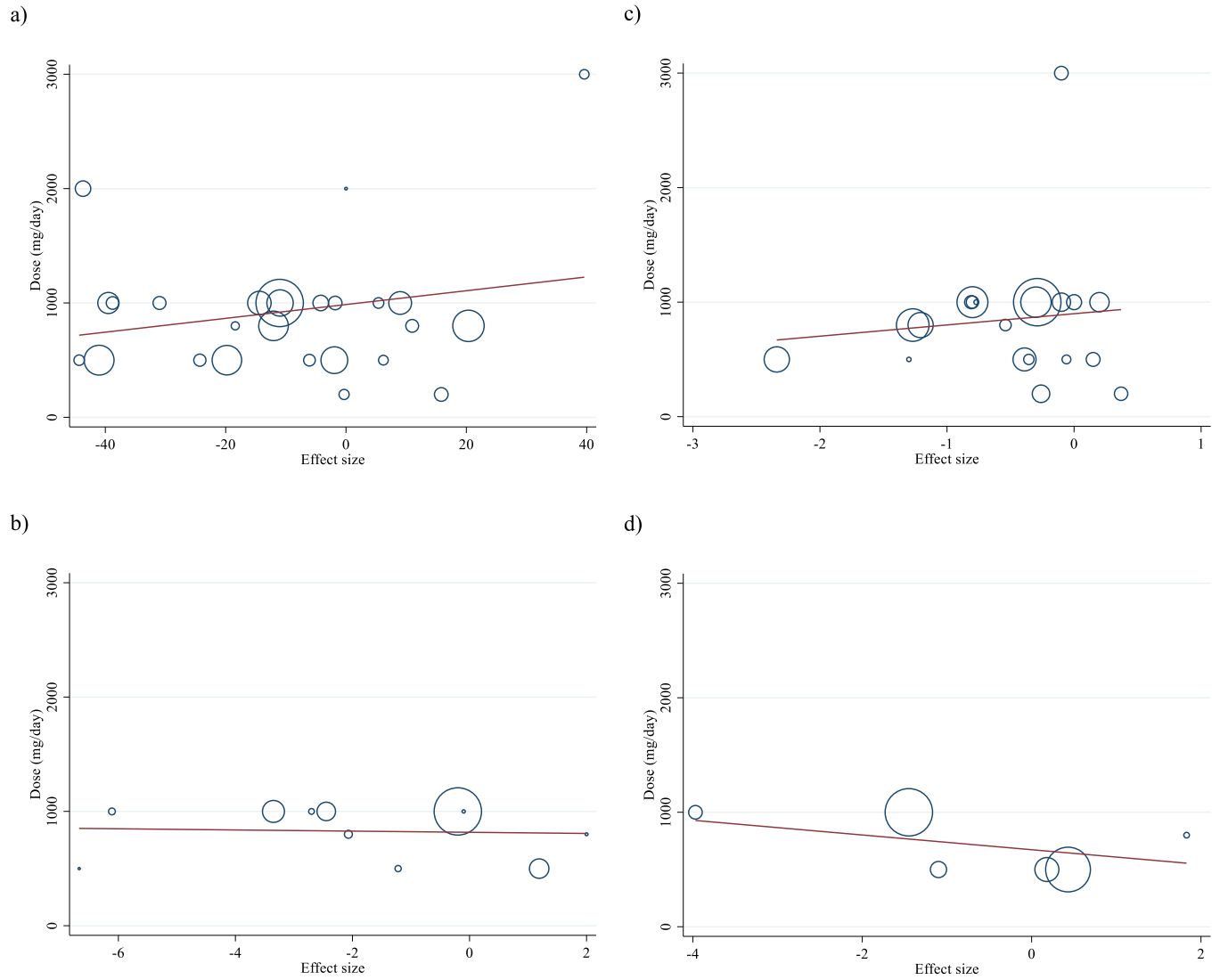


Fig. 5. Linear dose-response relations between daily dose (mg) of vitamin C supplementation and absolute mean differences in (a) fasting blood glucose (FBG), (b) fasting insulin, (c) hemoglobin A1c(HbA1c), and (d) homeostasis model assessment of insulin resistance (HOMA-IR).

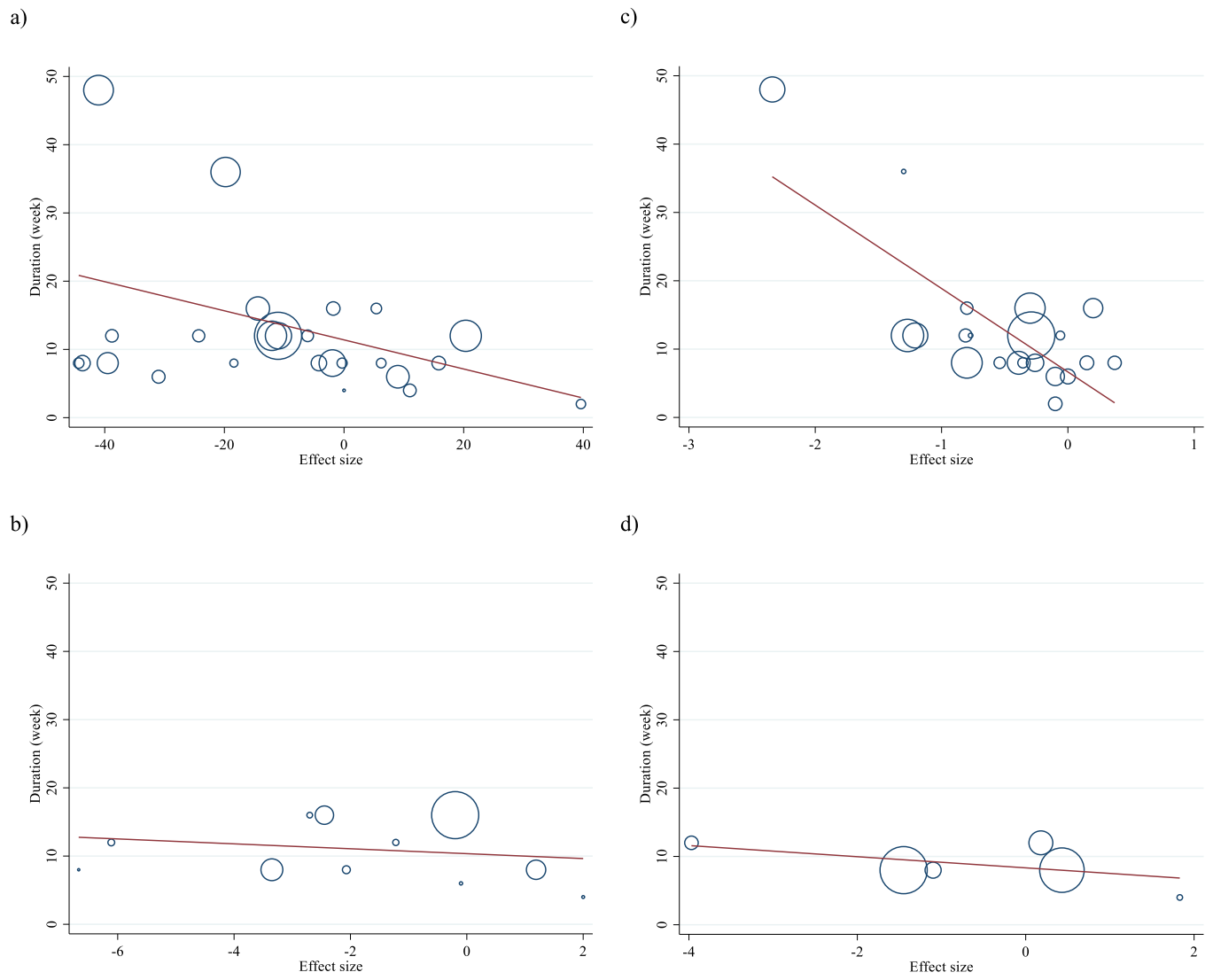


Fig. 6. Linear dose-response relations between intervention duration (weeks) of vitamin C supplementation and absolute mean differences in (a) fasting blood glucose (FBG), (b) fasting insulin, **(c)** hemoglobin A1c(HbA1c), and **(d)** homeostasis model assessment of insulin resistance (HOMA-IR).

C, leading to vitamin C depletion [56]. T2DM may also be associated with decreased renal reuptake of vitamin C, and diabetic patients with microalbuminuria may excrete more vitamin C in their urine [57].

Diabetes development is significantly associated with oxidative stress [58]. Hyperglycemia stimulates the production of free radicals, but it also impairs the endogenous antioxidant defense system [59]. Impaired cellular enzymes and organelles, raised lipid peroxidation, and the development of insulin resistance may result from high levels of free radicals and a reduced antioxidant defense capacity [59]. Consuming antioxidant-rich foods or taking antioxidant supplements may be a beneficial strategy for managing T2DM and other chronic diseases [60–62]. Furthermore, there is an inverse relationship between serum levels of vitamin C and the risk of T2DM [63]. These findings highlight the potential benefits of vitamin C supplementation in patients with T2DM.

In diabetes, high blood sugar levels lead to the production and development of reactive oxygen species (ROS), causing oxidative stress [64]. Oxidative stress is associated with dysfunction of beta cells and mitochondria, insulin resistance, and abnormal glucose tolerance [65]. Studies have identified various mechanisms by which ROS-induced insulin resistance occurs, including activation of c-Jun N-terminal protein kinase (JNK), reduction in glucose uptake, and increment of tumor necrosis factor-alpha (TNF-α) [66–68]. Vitamin C has been found to reduce both TNF-α gene expression and JNK activation, both in vitro and in vivo. The decrease in scavenger system efficiency, such as that of vitamin C, is the main cause of oxidative stress development [69], and thus vitamin C supplementation can help reduce oxidative stress in diabetic patients [59]. Inflammation also plays a role in insulin resistance and vitamin C administration has been shown to suppress the proinflammatory process by preventing the activation of nuclear factor-kappa B (NF-kB), which contributes to the development of chronic inflammation in T2DM patients [70,71].

The present meta-analysis had some limitations, including variations in supplement dosage, differences in sample characteristics of the studies, discrepancies in the timing of outcome measurements, and differences in the length of follow-up. There was also between-studies heterogeneity [72,73]. Additionally, most of the RCTs did not assess baseline serum AA or the dietary intake of vitamin C, which could be another source of heterogeneity due to differences in the vitamin C status of participants.

5. Conclusion

In summary, this meta-analysis explored a substantial decrease in serum HbA1c, fasting insulin, and FBG levels in vitamin C-treated T2DM patients compared with their untreated counterparts. The review

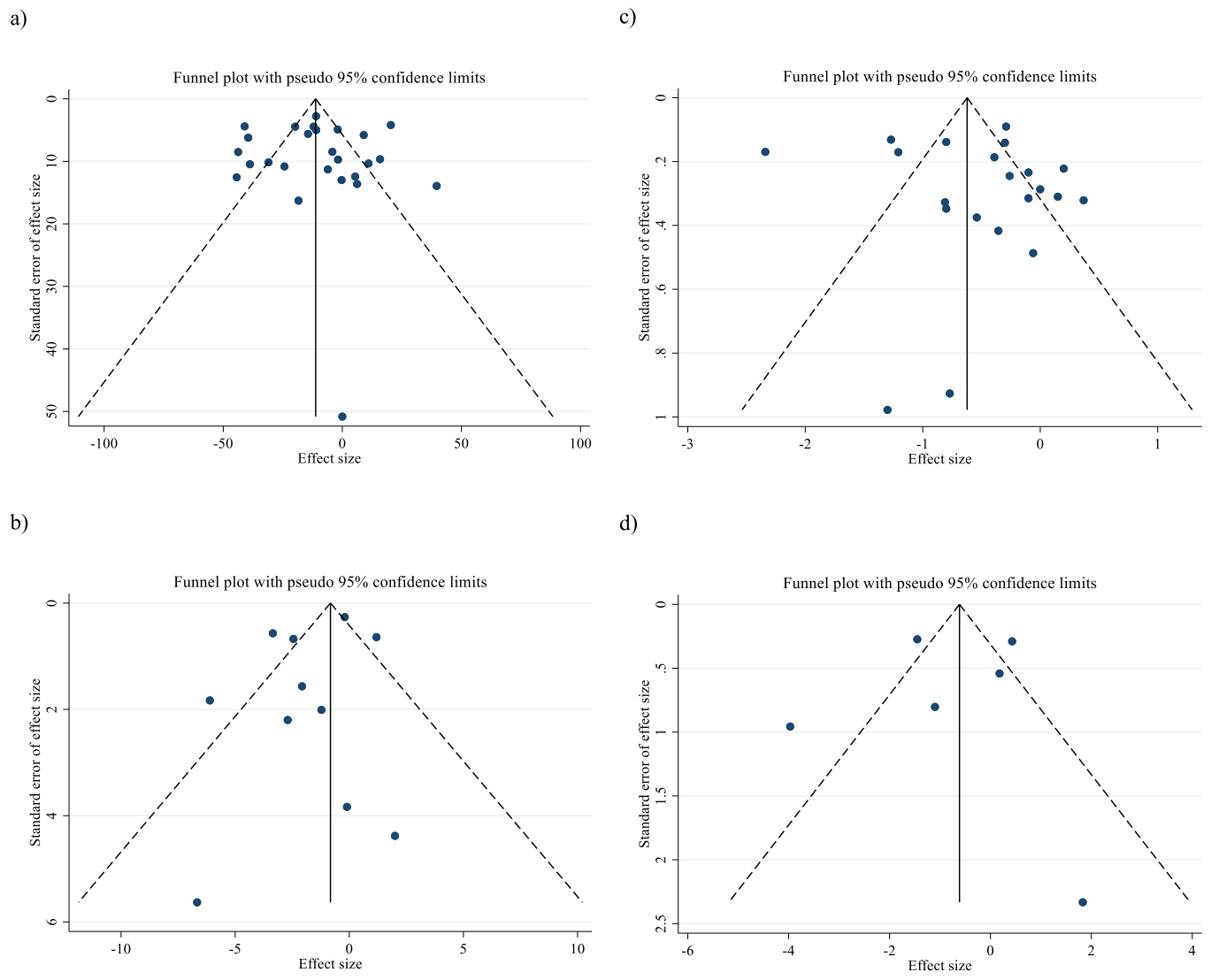


Fig. 7. Funnel plots for the effect of vitamin C supplementation on; a) FBG, b) fasting insulin, c) HbA1c, and d) HOMA-IR.

suggests that long-term (≥12 weeks) and high-dose vitamin C supplementation (≥1000 mg/d) could ameliorate glycemic profile in T2DM patients. Additional high-quality RCTs are required to confirm these findings.

Author contributions

OA, MZ, SN, and DAL designed the protocol of this study. ZN, FH, and OA contributed to the search, screening, and extraction of the data. OA analyzed the data. SHM, OA, DAL, and ZN provided the first draft of the manuscript. SHM participated in writing and editing the paper. AW-He had a significant contribution to the editing of the manuscript.. All authors have reviewed and approved the final draft of the manuscript.

Funding and support

None.

Declaration of competing interest

The authors have no conflicts of interest to declare.

References

[1] Roden M, Shulman GI. The integrative biology of type 2 diabetes. Nature 2019;576 (7785):51–60.
[2] Saeedi P, Petersohn I, Salpea P, et al. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: results from the international diabetes federation diabetes atlas. Diabetes Res Clin Pract 2019;157: 107843.
[3] Atlas D. International diabetes federation. *IDF diabetes atlas*. seventh ed. Brussels, Belgium: International Diabetes Federation; 2015.
[4] Stratton IM, Adler AI, Neil HAW, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. Bmj 2000;321(7258):405–12.
[5] Asbaghi O, Fouladvand F, Gonzalez MJ, Ashtary-Larky D, Choghakhori R, Abbasnezhad A. Effect of green tea on glycemic control in patients with type 2 diabetes mellitus: a systematic review and meta-analysis. Diabetes Metabol Syndr: Clin Res Rev 2021;15(1):23–31.
[6] Asbaghi O, Fouladvand F, Moradi S, Ashtary-Larky D, Choghakhori R, Abbasnezhad A. Effect of green tea extract on lipid profile in patients with type 2 diabetes mellitus: a systematic review and meta-analysis. Diabetes Metabol Syndr: Clin Res Rev 2020;14(4):293–301.
[7] Namkhah Z, Ashtary-Larky D, Naeini F, Clark CC, Asbaghi O. Does vitamin C supplementation exert profitable effects on serum lipid profile in patients with type 2 diabetes? A systematic review and dose-response meta-analysis. Pharmacol Res 2021;169:105665.
[8] Noormohammadi M, Eslamian G, Malek S, Shoaibinobarian N, Mirmohammadali SN. The association between fertility diet score and polycystic ovary syndrome: a Case-Control study. Health Care Women Int 2022;43(1–3): 70–84.

[9] Shoaibinobarian N, Eslamian G, Noormohammadi M, Malek S, Rouhani S, Mirmohammadali SN. Dietary total antioxidant capacity and risk of polycystic ovary syndrome: a case-control study. International Journal of Fertility and Sterility 2022;16(3):200–5.

[10] Paolisso G, Balbi V, Volpe C, et al. Metabolic benefits deriving from chronic vitamin C supplementation in aged non-insulin dependent diabetics. J Am Coll Nutr 1995;14(4):387–92.

[11] Jafari N, Shoaibinobarian N, Dehghani A, et al. The effects of purslane consumption on glycemic control and oxidative stress: a systematic review and dose–response meta-analysis. Food Science & Nutrition.[n/a(n/a)].

[12] Scott JA, King GLJ. Oxidative stress and antioxidant treatment in diabetes. Ann N Y Acad Sci 2004;1031(1):204–13.

[13] Tamari Y, Nawata H, Inoue E, et al. Protective roles of ascorbic acid in oxidative stress induced by depletion of superoxide dismutase in vertebrate cells. Free Radic Res 2013;47(1):1–7.

[14] Kaźmierczak-Barańska J, Boguszewska K, Adamus-Grabicka A, Karwowski BT. Two faces of vitamin C—antioxidative and pro-oxidative agent. Nutrients 2020;12(5):1501.

[15] Harding A-H, Wareham NJ, Bingham SA, et al. Plasma vitamin C level, fruit and vegetable consumption, and the risk of new-onset type 2 diabetes mellitus: the European prospective investigation of cancer–Norfolk prospective study. Arch Intern Med 2008;168(14):1493–9.

[16] Puvvada RC. Association of vitamin C status in diabetes mellitus: prevalence and predictors of vitamin C deficiency. Future Journal of Pharmaceutical Sciences 2020;6:1–5.

[17] Christie-David DJ, Girgis CM, Gunton JE. Effects of vitamins C and D in type 2 diabetes mellitus. Nutr Diet Suppl 2015;7:21–8.

[18] Eshak ES, Iso H, Muraki I, Tamakoshi A. Among the water-soluble vitamins, dietary intakes of vitamins C, B 2 and folate are associated with the reduced risk of diabetes in Japanese women but not men. Br J Nutr 2019;121(12):1357–64.

[19] Afkhami-Ardekani M, Shojaoddiny-Ardekani A. Effect of vitamin C on blood glucose, serum lipids & serum insulin in type 2 diabetes patients. Indian J Med Res 2007;126(5):471.

[20] Mahmoudabadi MMS, Djalali M, Djazayery SA, et al. Effects of eicosapentaenoic acid and vitamin C on glycemic indices, blood pressure, and serum lipids in type 2 diabetic Iranian males, vol. 16; 2011. p. S361. Suppl1.

[21] Mason SA, Rasmussen B, van Loon LJ, Salmon J, Wadley GD. Ascorbic acid supplementation improves postprandial glycaemic control and blood pressure in individuals with type 2 diabetes: findings of a randomized cross-over trial. Diabetes Obes Metabol 2019;21(3):674–82.

[22] Lu Q, Björkhem I, Wretlind B, Diczfalusy U, Henriksson P, Freyschuss A. Effect of ascorbic acid on microcirculation in patients with Type II diabetes: a randomized placebo-controlled cross-over study. Clin Sci 2005;108(6):507–13.

[23] Mason SA, Keske MA, Wadley GD. Effects of vitamin C supplementation on glycemic control and cardiovascular risk factors in people with type 2 diabetes: a GRADE-assessed systematic review and meta-analysis of randomized controlled trials. Diabetes Care 2021;44(2):618–30.

[24] Evans M, Anderson R, Smith J, et al. Effects of insulin lispro and chronic vitamin C therapy on postprandial lipaemia, oxidative stress and endothelial function in patients with type 2 diabetes mellitus. Eur J Clin Invest 2003;33(3):231–8.

[25] Hamed AT, Al Zinati SM, Al Swirky A. The effect of vitamin C alone or in combination with vitamin E on fasting blood glucose, glycosylated hemoglobin and lipid profile in type 2 diabetic patients (Gaza strip). Jordan Journal of Pharmaceutical Sciences 2016;9(1):1–12.

[26] Nayaka R. A comparative trial on the efficacy of vitamin c as add on therapy to the oral hypoglycemic agent on serum lipid level in newly diagnosed type 2 diabetes mellitus. IJPR 2015;5(4):115.

[27] Page MJ, Moher D, Bossuyt P, et al. PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. 2020.

[28] Higgins JP, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. Bmj 2011;343.

[29] Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. Bmj 2008;336(7650):924–6.

[30] Borenstein M, Hedges LV, Higgins JP, Rothstein HR. Introduction to meta-analysis. John Wiley & Sons; 2021.

[31] DerSimonian R, Laird N. Meta-analysis in clinical trials control clin trials, vol. 177; 1986. 10.

[32] Borenstein M, Hedges LV, Higgins JP, Rothstein HR. A basic introduction to fixed-effect and random-effects models for meta-analysis. Res Synth Methods 2010;1(2):97–111.

[33] Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. Bmj 2003;327(7414):557–60.

[34] Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. Bmj 1997;315(7109):629–34.

[35] Mitchell MN. Interpreting and visualizing regression models using Stata, vol. 558. College Station, TX: Stata Press; 2012.

[36] Chen H, Karne RJ, Hall G, et al. High-dose oral vitamin C partially replenishes vitamin C levels in patients with Type 2 diabetes and low vitamin C levels but does not improve endothelial dysfunction or insulin resistance. Am J Physiol Heart Circ Physiol 2006;290(1):H137–45.

[37] Tousoulis D, Antoniades C, Vasiliadou C, et al. Effects of atorvastatin and vitamin C on forearm hyperaemic blood flow, asymmentrical dimethylarginine levels and the inflammatory process in patients with type 2 diabetes mellitus. Heart 2007;93(2):244–6.

[38] Dakhale GN, Chaudhari HV, Shrivastava M. Supplementation of vitamin C reduces blood glucose and improves glycosylated hemoglobin in type 2 diabetes mellitus: a randomized, double-blind study. Advances in pharmacological sciences 2011;2011.

[39] Rafighi Z, Arab S, Yusof RM, Shiva A. The effect of vitamin C and E on lipid profile in people with type 2 diabetes mellitus. Global J Health Sci 2011;3(2):69.

[40] Bhatt JK, Thomas S, Nanjan M. Effect of oral supplementation of vitamin C on glycemic control and lipid profile in patients with type 2 diabetes mellitus. Int J Pharm Pharmaceut Sci 2012;4(2):524–7.

[41] Siavash M, Amini M. Vitamin C may have similar beneficial effects to Gemfibrozil on serum high-density lipoprotein-cholesterol in type 2 diabetic patients. J Res Pharm Pract 2014;3(3):77.

[42] Ghaffari P, Nadiri M, Gharib A, Rahimi F. The effects of vitamin C on diabetic patients. Der Pharm Lett 2015;7(10):68–71.

[43] Mason SA, Della Gatta PA, Snow RJ, Russell AP, Wadley GD. Ascorbic acid supplementation improves skeletal muscle oxidative stress and insulin sensitivity in people with type 2 diabetes: findings of a randomized controlled study. Free Radic Biol Med 2016;93:227–38.

[44] Sanguanwong S, Tangvarasittichai O, Sengsuk C, Tangvarasittichai S. Oral supplementation of vitamin C reduced lipid peroxidation and insulin resistance in patients with type 2 diabetes mellitus. International Journal of Toxicological and Pharmacological Research 2016;8(3):114–9.

[45] Gillani SW, Sulaiman SAS, Abdul MIM, Baig MR. Combined effect of metformin with ascorbic acid versus acetyl salicylic acid on diabetes-related cardiovascular complication; a 12-month single blind multicenter randomized control trial. Cardiovasc Diabetol 2017;16(1):103.

[46] Abd El-Aal A, Abd El-Ghffar EA, Ghali AA, Zughbur MR, Sirdah MM. The effect of vitamin C and/or E supplementations on type 2 diabetic adult males under metformin treatment: a single-blinded randomized controlled clinical trial. Diabetes Metabol Syndr: Clin Res Rev 2018;12(4):483–9.

[47] Froghi M, Ghatreh SK, Heidarian E, Nikokar M, Fazeli S. Study effects of resveratrol, cuminumcyminum, essence and vitamin C on blood sugar, lipid, insulin resistance and advanced glycatedend product (AGEs) in type2 diabetic patients. 2018.

[48] Kunsongkeit P, Okuma N, Rassameemasmaung S, Chaivanit P. Effect of vitamin C as an adjunct in nonsurgical periodontal therapy in uncontrolled type 2 diabetes mellitus patients. Eur J Dermatol 2019;13(3):444.

[49] Devanandan P, Puvvada Rc, Muthukumar Va. Effects of vitamin C supplementation on the glycemic control and cardiovascular risk in Type II Diabetes Mellitus. 2020.

[50] Ragheb SR, El Wakeel LM, Nasr MS, Sabri NA. Impact of Rutin and Vitamin C combination on oxidative stress and glycemic control in patients with type 2 diabetes. Clinical Nutrition ESPEN 2020;35:128–35.

[51] Mahmoudabadi MMS, Djalali M, Djazayery SA, et al. Effects of eicosapentaenoic acid and vitamin C on glycemic indices, blood pressure, and serum lipids in type 2 diabetic Iranian males. J Res Med Sci: the official journal of Isfahan University of Medical Sciences 2011;16(Suppl1):S361.

[52] Lu Q, Björkhem I, Wretlind B, Diczfalusy U, Henriksson P, Freyschuss AJCS. Effect of ascorbic acid on microcirculation in patients with Type II diabetes: a randomized placebo-controlled cross-over study, vol. 108; 2005. p. 507–13. 6.

[53] Ashor A, Werner A, Lara J, Willis N, Mathers J, MjejoCN Siervo. Effects of vitamin C supplementation on glycaemic control: a systematic review and meta-analysis of randomised controlled trials, vol. 71; 2017. p. 1371–80. 12.

[54] Shim JE, Paik HY, Shin CS, Park KS, Lee HKJ. Vitamin C nutriture in newly diagnosed diabetes. J Nutr Sci Vitaminol 2010;56(4):217–21.

[55] Gokhale NH, Acharya AB, Patil VS, Trivedi DJ, Thakur SLJJods. A short-term evaluation of the relationship between plasma ascorbic acid levels and periodontal disease in systemically healthy and type 2 diabetes mellitus subjects, vol. 10; 2013. p. 93–104. 2.

[56] Christie-David DJ, Girgis CM, Gunton JEJN, Supplements D. Effects of vitamins C and D in type 2 diabetes mellitus, vol. 7; 2015. p. 21–8.

[57] Ebenuwa I, Violet P-C, Padayatty S, et al. Abnormal urinary loss of vitamin C in diabetes: prevalence and clinical characteristics of a vitamin C renal leak. Am J Clin Nutr 2022;116(1):274–84.

[58] Volpe CMO, Villar-Delfino PH, dos Anjos PMF, Nogueira-Machado JA. Cellular death, reactive oxygen species (ROS) and diabetic complications. Cell Death Dis 2018;9(2):119.

[59] Maritim A, Sanders a, Watkins Iii J. Diabetes, oxidative stress, and antioxidants: a review. J Biochem Mol Toxicol 2003;17(1):24–38.

[60] Asbaghi O, Choghakhori R, Abbasnezhad A. Effect of Omega-3 and vitamin E co-supplementation on serum lipids concentrations in overweight patients with metabolic disorders: a systematic review and meta-analysis of randomized controlled trials. Diabetes Metabol Syndr: Clin Res Rev 2019;13(4):2525–31.

[61] Asbaghi O, Nazarian B, Reiner Ž, et al. The effects of grape seed extract on glycemic control, serum lipoproteins, inflammation, and body weight: a systematic review and meta-analysis of randomized controlled trials. Phytother Res 2020;34(2):239–53.

[62] Eslampour E, Asbaghi O, Hadi A, et al. The effect of almond intake on blood pressure: a systematic review and meta-analysis of randomized controlled trials. Compl Ther Med 2020;50:102399.

[63] Liu C, Zhong C, Chen R, et al. Higher dietary vitamin c intake is associated with a lower risk of gestational diabetes mellitus. A longitudinal cohort study 2020;39(1):198–203.

[64] Babel RA, Mpjcdr Dandekar. A review on cellular and molecular mechanisms linked to the development of diabetes complications. 2020.

[65] Rains JL, Jain SK. Medicine. Oxidative stress, insulin signaling, and diabetes, 50; 2011. p. 567–75. 5.

[66] Kyaw M, Yoshizumi M, Tsuchiya K, Kirima K, Tamaki TJHR. Antioxidants inhibit JNK and p38 MAPK activation but not ERK 1/2 activation by angiotensin II in rat aortic smooth muscle cells, vol. 24; 2001. p. 251–61. 3.
[67] Ji Y-L, Wang Z, Wang H, et al. Ascorbic acid protects against cadmium-induced endoplasmic reticulum stress and germ cell apoptosis in testes, vol. 34; 2012. p. 357–63. 3.
[68] Canali R, Natarelli L, Leoni G, et al. Vitamin C supplementation modulates gene expression in peripheral blood mononuclear cells specifically upon an inflammatory stimulus: a pilot study in healthy subjects, vol. 9; 2014. p. 390. 3.
[69] Bravi MC, Armiento A, Laurenti O, et al. Insulin decreases intracellular oxidative stress in patients with type 2 diabetes mellitus, vol. 55; 2006. p. 691–5. 5.
[70] Dandona P, Aljada A, Bandyopadhyay AJTii. Inflammation: the link between insulin resistance. obesity and diabetes 2004;25(1):4–7.
[71] Son E-W, Mo S-J, Rhee D-K, Sjaopr Pyo. Vitamin C blocks TNF-α-induced NF-kB activation and ICAM-1 expression in human neuroblastoma cells, vol. 27; 2004. p. 1073. 10.
[72] Sandercock PJCD. The authors Say:'The data are not so robust because of heterogeneity'–so, how should I deal with this systematic review?, vol. 31; 2011. p. 615–20. 6.
[73] Higgins JP, Thomas J, Chandler J, et al. Cochrane handbook for systematic reviews of interventions. John Wiley & Sons; 2019.