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

AUTHOR(S)

Shaun Mason, Michelle Keske, Glenn Wadley

PUBLICATION DATE

01-02-2021

HANDLE

10536/DRO/DU:30147432

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

Shaun A. Mason,[1] Michelle A. Keske,[2] and Glenn D. Wadley[2]

Diabetes Care 2021;44:618–630 | https://doi.org/10.2337/dc20-1893

META-ANALYSIS

BACKGROUND

Evidence suggests that vitamin C supplementation could be a potential therapy in type 2 diabetes. However, its effectiveness and evidence quality require further evaluation.

PURPOSE

To investigate the efficacy of oral vitamin C supplementation in improving glycemic control, cardiovascular risk factors, and oxidative stress in people with type 2 diabetes.

DATA SOURCES

Databases (PubMed, Embase, Scopus, Cochrane Library) and clinical trial registries were searched for randomized controlled trials up to 8 September 2020.

STUDY SELECTION

Trials in adults with type 2 diabetes were included. Trials were excluded if supplements were not exclusive to vitamin C and if <2 weeks in duration.

DATA EXTRACTION

Primary outcomes were HbA_{1c}, glucose, cholesterol, triglycerides, and blood pressure (BP). Data were extracted for changes in outcomes between vitamin C and control groups. Evidence certainty was assessed using Grading of Recommendations, Assessment, Development, and Evaluation methods.

DATA SYNTHESIS

Twenty-eight studies (N = 1,574 participants) were included in the review. Outcomes that changed to a statistically and clinically significant extent with vitamin C were systolic BP (mean difference −6.27 [95% CI −9.60, −2.96] mmHg; P = 0.0002), with moderate evidence certainty, and HbA_{1c} (−0.54% [−0.90, −0.17]; P = 0.004) and diastolic BP (−3.77 [−6.13, −1.42] mmHg; P = 0.002) with very low evidence certainty.

LIMITATIONS

Studies were predominantly short term (<6 months) with a small number of participants (n < 100).

[1]School of Exercise and Nutrition Sciences, Deakin University, Melbourne, Victoria, Australia
[2]Institute for Physical Activity and Nutrition, School of Exercise and Nutrition Sciences, Deakin University, Geelong, Victoria, Australia

Corresponding author: Shaun A. Mason, s.mason@deakin.edu.au

Received 29 July 2020 and accepted 30 October 2020

This article contains supplementary material online at https://doi.org/10.2337/figshare.13171967.

CONCLUSIONS

While evidence from short-term studies suggests that vitamin C supplementation may improve glycemic control and BP in people with type 2 diabetes, vitamin C supplementation cannot currently be recommended as a therapy until larger, long-term, and high-quality trials confirm these findings.

Type 2 diabetes remains a serious driver of chronic diseases, including cardiovascular disease. Improving glycemic control is important for managing type 2 diabetes; however, improving blood pressure (BP), lipid levels, and insulin sensitivity are also important targets to reduce the risk of cardiovascular disease in type 2 diabetes (1). Excess reactive oxygen species and oxidative stress are among the pathophysiological factors underlying impaired glucose metabolism and vascular complications of type 2 diabetes (2,3). Emerging evidence from predominantly short-term and small randomized controlled trials (RCTs) has suggested that antioxidant therapy may be effective in improving glycemic control and cardiovascular risk factors in people with type 2 diabetes (4–7).

Vitamin C is a water-soluble antioxidant that has been investigated therapeutically in people with type 2 diabetes. Prior systematic reviews of RCTs have focused on the effects of vitamin C supplementation on glycemic control (8), lipids (9), BP (10), and endothelial function (11), although these were not specific to people with type 2 diabetes. Other meta-analyses investigated effects of vitamins in people with type 2 diabetes (12–14); however, supplements were not exclusive to vitamin C only. While these prior reviews included many relevant studies, the substantial increase in published studies over recent years warrants an updated and more focused evaluation of vitamin C supplementation on cardiometabolic risk factors in people with type 2 diabetes. Furthermore, limited information on evidence quality and evidence certainty also warrants further evaluation to ascertain potential clinical translatability of vitamin C supplementation. The aim of this review, therefore, is *1*) to investigate the efficacy of oral vitamin C supplementation in improving glycemic control, blood lipids, BP, and oxidative stress in people with type 2 diabetes and *2*) to assess evidence certainty on the basis of the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach.

RESEARCH DESIGN AND METHODS

Data Searches and Sources

A systematic review and meta-analysis of RCTs (PROSPERO registry CRD42019140113) was undertaken, targeting effects of oral vitamin C supplementation on primary outcomes of glycemic control (HbA_{1c}, fasting glucose), blood lipids (triglycerides, total cholesterol, HDL cholesterol, LDL cholesterol), and BP (systolic, diastolic). Secondary outcomes were postprandial glucose, fasting insulin, HOMA of insulin resistance (HOMA-IR), clamp insulin sensitivity, and oxidative stress markers. Databases searched were Cochrane Library, Scopus, Embase, and MEDLINE-PubMed. Clinical trial registries (ClinicalTrials.gov, ANZCTR, EU Clinical Trial Register, and ISRCTN) were also searched for additional completed studies. Searches were not limited to English-language records. Database and registry searches were conducted three times from 5 September 2019 to 8 September 2020. Specific search strategies used are outlined in Supplementary Table 1.

Study Selection

Studies included were RCTs involving participants with type 2 diabetes. Exclusion criteria included comparisons that used intravenous (or nonoral) vitamin C administration, involved participants with type 1 diabetes, involved participants who were pregnant or $<$18 years old, lacked a control group, included other supplements besides vitamin C, and were $<$2 weeks in duration.

The selection of the studies was performed by two reviewers (S.A.M. and G.D.W.) independently using Covidence systematic review software (Veritas Health Innovation, Melbourne, Victoria, Australia). Studies were screened on the basis of their titles and abstracts. Studies that could not be ruled out had their full texts evaluated, and their eligibility was determined. Any discrepancies during selection of studies were resolved by reviewer consensus, although if a consensus could not be reached, a third reviewer (M.A.K.) adjudicated the decision.

Data Extraction and Quality Assessment

The following data were extracted from selected RCTs by two reviewers (S.A.M. and G.D.W.) independently: author, publication year, study design, number of subjects per arm, losses per arm, sex, mean age, mean BMI, mean duration of diabetes, duration of supplementation, dose/dosage regimen, baseline vitamin C concentration, baseline HbA_{1c}, diabetes and other medications, and outcome data. Quantitative and qualitative reports on adverse effects observed were also recorded.

Any discrepancies during data extraction were resolved by reviewer consensus, although if a consensus could not be reached, a third reviewer (M.A.K.) adjudicated the decision. Authors of studies were contacted in instances where full-text articles could not be obtained or if data were unclear in the articles. Two full-text studies could not be obtained (15,16), and accurate BP values could not be established for two studies (17,18). The latter studies were subsequently excluded from BP analyses.

The Cochrane risk-of-bias tool (19) was used to evaluate bias in studies, including domains of random sequence generation, allocation concealment, blinding of participants and researchers, blinding of outcome assessment, incomplete outcome data, and selective reporting. Other biases, including compliance with treatment and diet and lifestyle confounding, were also assessed. Two reviewers (S.A.M. and G.D.W.) evaluated biases independently, with any discrepancies adjudicated by consensus.

Data Synthesis and Analysis

Between-group differences in (within-group) pre-post changes were determined for outcomes. For parallel design trials, mean pre-post differences and SDs were used or calculated from the pretreatment and posttreatment data. If not provided, the pre-post change SD was calculated assuming a correlation coefficient of 0.7. This value was established on the basis of correlation coefficient values determined using data from two studies in our review (5,20). We also undertook sensitivity analyses of all outcomes using a correlation coefficient value of 0.5 for which no changes in statistical outcomes occurred compared with use of a 0.7 correlation coefficient (Supplementary Table 2). One study (21) did not provide

variance data, and for that study, SD values consistent with average vitamin C and control group data across all other included studies were imputed.

Crossover trials were regarded similarly to parallel trials, with separate vitamin C and control arms. One crossover study (22) did not provide pretreatment values, and therefore, for that study, only posttreatment data were used.

Three studies (21–23) included multiple vitamin C groups with different doses. For these studies, all vitamin C groups were combined into a single group, with collective means and SDs determined according to recommended methods (24). Other studies (23,25–28) did not include posttreatment data for some outcomes. These studies were not included in the main analyses; however, they were included in sensitivity analyses, where pretreatment data were carried forward as posttreatment data. Significant results of main analyses were not affected by inclusion of these studies (Supplementary Table 2).

Pooled estimates and 95% CIs of effect sizes were calculated using random-effects modeling with DerSimonian-Laird methods in Review Manager software (29). Heterogeneity between studies was assessed using Cochran Q and I^2 statistics. Ninety-five percent prediction intervals (95% PIs) were additionally calculated to highlight study heterogeneity. A 95% PI estimates where the possible effects of vitamin C supplementation are to be expected for 95% of similar studies that might be conducted in the future (30). Mean difference (MD) effect sizes were used for all outcomes except clamp insulin sensitivity and oxidative stress outcomes, for which standardized MDs were used to account for significant variations in measurements/methods used. Data generated from Review Manager software were used to generate forest plots with Stata IC 16.1 software (StataCorp, College Station, TX). $P < 0.05$ was used to establish statistical significance for all statistical tests used.

Subgroup and meta-regression analyses were conducted on outcome measures that contained at least 10 studies. Prespecified subgroup analyses were based on BMI (nonobese <30 kg/m^2 vs. obese ≥ 30 kg/m^2), plasma vitamin C concentration (hypovitaminosis C <23 μmol/L vs. ≥ 23 μmol/L), vitamin C dose used (lower dose $<1{,}000$ mg/day vs. high dose $\geq 1{,}000$ mg/day), and treatment duration (shorter term <12 weeks vs. longer term ≥ 12 weeks). The rationale for these analyses was to assess potential sources of heterogeneity and to identify possible subgroups of differing vitamin C efficacy. Post hoc subgroup analyses investigating the potential impact of the control comparator group (active control vs. placebo) and overall study risk of bias (four or more of seven low-risk domains of bias vs. fewer than four of seven low-risk domains of bias) on outcomes were also undertaken. Heterogeneity as a result of potential modifying effects of various factors were further explored in (post hoc) meta-regression analyses using Stata software. Baseline biological factors of HbA_{1c}, BMI, age, duration of diabetes, and vitamin C concentration may plausibly affect the relative efficacy of treatment as explored previously (8–10), while trial-related factors, such as vitamin C dose, treatment duration, and study participant number, might further explain heterogeneity and efficacy of outcomes (8–10). Sensitivity analyses were conducted to evaluate only low-risk-of-bias studies on the basis of individual Cochrane risk-of-bias domains (Supplementary Table 2).

GRADEpro GDT software (31) was used to assess certainty of evidence for primary outcomes on the basis of areas of study design, risk of bias, inconsistency, indirectness, imprecision, and other considerations, such as publication bias, effect size, and potential confounding. Grades of evidence and their explanations include the following:

- High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
- Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
- Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect (32).

We regarded a threshold of $I^2 > 50\%$ to denote inconsistency. For imprecision, we rated outcomes down if 95% CIs overlapped with nonclinically important effects. Minimal thresholds of clinically important changes considered were HbA_{1c} $\geq 0.5\%$ (33), fasting glucose ≥ 1 mmol/L (34), total cholesterol ≥ 1 mmol/L (35), LDL cholesterol ≥ 0.3 mmol/L (36), HDL cholesterol ≥ 0.03 mmol/L (37), triglycerides ≥ 1 mmol/L, and systolic BP (SBP) and diastolic BP (DBP) >2 mmHg (38). We rated evidence certainty of outcomes down for risk of bias if sensitivity analyses investigating only low-risk studies on the basis of individual Cochrane risk-of-bias domains yielded inconsistent statistical outcomes across domains. We also rated evidence certainty of outcomes down for indirectness because our primary outcomes are surrogate rather than patient-important outcomes (39).

Publication Bias

Small study effects were assessed using funnel plots and the Egger regression test when there were at least 10 studies, including at least 1 medium/large sample study (40).

RESULTS

Of 2,318 studies identified for screening, 68 full-text articles were reviewed in depth (Supplementary Fig. 1). Of these studies, 28 were deemed eligible for inclusion in the review (Table 1). Clinical trial registry searches yielded no additional studies to those found published in the searched databases. The main reasons for study exclusion were the wrong study design, repeat or redundant data, and the wrong participant population. Only eight studies (5,6,20,41–45) were rated as low risk in at least four of seven Cochrane risk-of-bias domains (Supplementary Fig. 2).

Vitamin C supplementation decreased HbA_{1c} to a statistically and clinically significant degree (MD -0.54% [95% CI -0.90, -0.17%]; $P = 0.004$ [95% PI -2.02, 0.94%]; $n = 1{,}133$ in 16 studies) (Fig. 1*A*), whereas fasting glucose was decreased to a statistically significant but not a clinically significant degree (MD -0.74 [95% CI -1.17, -0.31] mmol/L; $P = 0.0007$ [95% PI -2.44, 0.96 mmol/L]; $n = 1{,}305$ in 19 studies) (Fig. 1*B*) compared with control. Vitamin C also decreased postprandial glucose to a statistically significant degree (MD -0.95 [95% CI -1.83, -0.06] mmol/L; $P = 0.04$ [95% PI -4.67, 2.77 mmol/L];

Table 1—Studies included in the systematic review

Reference	Size, *n*	Study location	Male/female, *n*	Mean age (years)	Design	Length (days)	Total daily vitamin C (mg)	Control type	Mean BMI (kg/m^2)	Mean diabetes duration (years)	Mean HbA_{1c} (%) (mmol/mol)	Treatment			Baseline vitamin C (μmol/L)	Dropouts, *n*
												Diabetes	BP lowering‡	Lipid lowering§		
Bhatt et al. (56)	65	India	42/17	60.3	P, UB	90	500	Active control	25.4	7.5	9.1 (76)	OHA	NS	NS	NS	6
Chen et al. (44)	32	U.S.	13/19	47.9	P, DB	28	800	Placebo	35.1	5.6	7.9 (63)	NS	0 of 32	NS	22.5	5
Dakhale et al. (41)	70	India	28/38	47.1	P, DB	84	1,000	Placebo	NS	NS	8.2 (66)	MET 500 mg 2 × per day	NS	NS	14.2	4
Darko et al. (27)	35	U.K.	23/12	56	P, DB	21	1,500	Placebo	29	8.53	8.6 (70)	OHA	14 of 35	NS	54.6	0
Devanandan et al. (49)	148	India	84/51	44.92	P, SB?	270	1,000	Placebo	23.75	3.35	9.7 (82)	MET 500 mg 2 × per day	NS	NS	29.3	13
El-Aal et al. (50)	40 (20)¶	Palestine	40 male	51.02	P, SB	90	1,000	Placebo	31.65	3.08	8.1 (65)	MET 500 mg 2 × per day	NS	0 of 40	NS	0
Foroghi et al. (48)	154 (78)¶	Iran	41/37	56.67	P, DB	60	500	Placebo	27.51	NS	6.8 (51)	MET	NS	NS	NS	11 (total)
Ghaffari et al. (57)	40	Iran	13/18	51.9	P, SB	60	800	Placebo	NS	10.7	NS	OHA or diet	NS	NS	NS	9
Gillani et al. (18)	456 (304)¶	Malaysia	183/121	38	P, SB	365	500	Placebo	23.9	2.67	9.2 (77)	MET	0 of 456	0 of 456	NS	23
Gutierrez et al. (22)	8	U.S.	4/4	49	X, SB	14	250, 500, or 1,000	Placebo	29.4	4	6.6 (49)	OHA or diet	NS	NS	46	0
Kunsongkeit et al. (46)	31	Thailand	9/22	58.9	X, DB	60	500	Placebo	NS	7.75	8.0 (64)	NS	NS	NS	19.3	0
Lu et al. (43)	20	Sweden	12/5	54	X, DB	14	3,000	Placebo	NS	7	6.5 (48)	Diet, insulin or OHA	5 of 20	4 of 20	22.2	3
Mahmoudabadi et al. (17)	69 (34)¶	Iran	34 male	51.45	P, DB	56	200	Placebo	29.1	NS	7.9 (63)	NS	NS	NS	NS	4 (total)
Mahmoudabadi et al. (45)	81 (40)¶	Iran	40 male	51.5	P, DB	56	200	Placebo	29	NS	7.9 (63)	NS	0 of 81	0 of 81	14.2	0
Mason et al. (42)	13	Australia	12/1	57.9	X, DB	120	1,000	Placebo	30.5	5.2	7.6 (60)	OHA or diet	NS	NS	52.3	6
Mason et al. (5)	31	Australia	26/5	61.8	X, DB	120	1,000	Placebo	29.1	5.6	7.6 (60)	OHA or diet/ lifestyle	14 of 31	18 of 31	41.2	4
Mazloom et al. (58)	30	Iran	8/22	46.8	P, SB	42	1,000	Placebo	27.8	4.74	NS	OHA or diet	NS	NS	NS	3
Mullan et al. (25)	30	U.K.	22/8	59.45	P, DB	28	500	Placebo	28.6	<10	8.1 (65)	OHA	16 of 30	NS	43.3	0
Paolisso et al. (6)	40	Italy	19/21	72	X, DB	120	1,000	Placebo	27.7	8.1	8.1 (65)	OHA or diet	NS	NS	41.2	0
Rafighi et al. (59)	170 (84)¶	Iran	40/44	53.82	P, SB	90	800	Placebo	29.89	NS	8.4 (68)	OHA	NS	NS	NS	0
Ragheb et al. (51)	70 (45)¶	Egypt	10/23	56.42	P, UB	56	500	Active control	33.6	NS	8.7 (72)	OHA	NS	NS	NS	12

Continued on p. 622

Table 1—Continued

Reference	Size, *n*	Study location	Male/female, *n*	Mean age (years)	Design	Length (days)	Total daily vitamin C (mg)	Control type	Mean BMI (kg/m^2)	Mean diabetes duration (years)	Mean HbA_{1c} (%) (mmol/mol)	Treatment			Baseline vitamin C (μmol/L)	Dropouts, *n*
												Diabetes	BP lowering‡	Lipid lowering§		
Rekha et al. (21)	90	India	NS	47.86	P, UB	56	1,000 or 2,000	Active control	26.73	Newly diagnosed	NS	5 mg glibenclamide‖	NS	NS	NS	7
Sanguanwong et al. (20)	100	Thailand	NS	57.47	P, DB	60	1,000	Placebo	25.65	7.67	7.7 (61)	OHA	NS	NS	NS	0
Shateri et al. (26)	98	Iran	42/42	58	P, DB	45	1,000	Placebo	30.05	8.94	NS	NS	NS	NS	NS	14
Siavash and Amini (47)	67 (44)¶	Iran	12/18 (final)	53	P, SB	42	1,000	Active control	26.75	NS	6.6 (49)	NS	NS	67 of 67	NS	14
Tessier et al. (23)	36	Canada	8/28	71.67	P, DB	84	500 or 1,000	Placebo	29.4	9.47	7.4 (57)	OHA or insulin	NS	NS	NS	0
Tousoulis et al. (60)	41 (26)¶	Greece	14/12	60	P, SB	28	2,000	Active control	28.55	8.15	6.5 (48)	NS	NS	0 of 41	NS	0
Upritchard et al. (28)	57 (25)¶	New Zealand	16/9	58.08	P, SB?	28	500	Placebo	31.27	2.58	6.7 (50)	OHA or diet	NS	0 of 41	32.54	5 (total)

DB, double blinded; MET, metformin; NS, not specified; OHA, oral hypoglycemic agent; P, parallel study; SB, single blinded; UB, unblinded; X, crossover. ‡Proportion of participants on BP-lowering medications. §Proportion of participants on lipid-lowering medications. ¶Subtotal of participants relevant to this comparison. ‖Taken by both vitamin C and control groups.

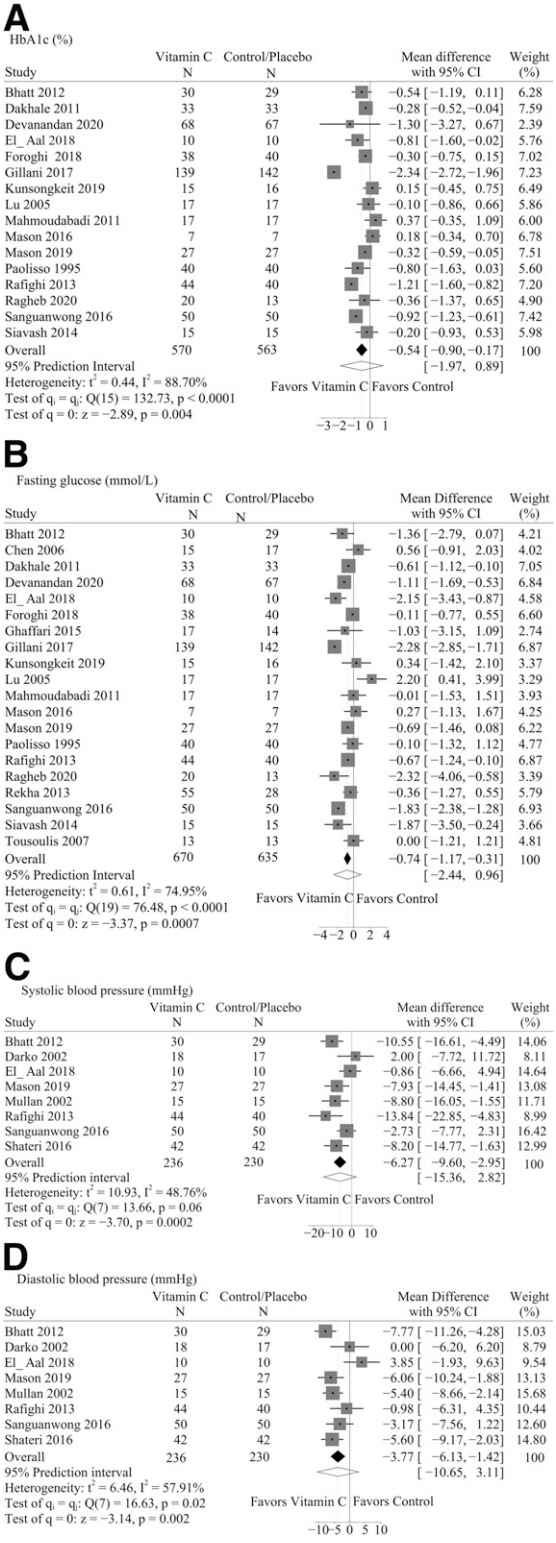

Figure 1—Forest plots of effect of vitamin C supplementation on primary glycemic control and BP outcomes in people with type 2 diabetes. Effects on HbA_{1c} (*A*), fasting glucose (*B*), SBP (*C*), and DBP (*D*).

n = 235 in four studies) (Supplementary Fig. 3) but had no significant effects on fasting insulin, HOMA-IR, or clamp insulin sensitivity (Supplementary Fig. 3) compared with control.

Vitamin C supplementation decreased SBP (MD −6.27 [95% CI −9.60, −2.96] mmHg; *P* = 0.0002 [95% PI −15.36, 2.82 mmHg]; *n* = 466 in eight studies) (Fig. 1*C*) and DBP (MD −3.77 [95% CI −6.13, −1.42] mmHg; *P* = 0.002 [95% PI −10.65, 3.11 mmHg]; *n* = 466 in eight studies) (Fig. 1*D*) to a statistically and clinically significant degree compared with control. A study excluded from BP analyses reported changes in BP as a proportion of participants above or below the threshold of 130/80 mmHg (18). Although raw data were not provided, that study showed a decrease in the proportion of participants above 130/80 mmHg from 88.8 to 42.1% after 12 months of vitamin C supplementation compared with a change from 92.1 to 83.5% after placebo supplementation.

Vitamin C supplementation decreased triglycerides (MD −0.20 [95% CI −0.36, −0.04] mmol/L; *P* = 0.01 [95% PI −0.79, 0.39 mmol/L]; *n* = 1,065 in 17 studies) (Fig. 2*A*) and total cholesterol (MD −0.27 [95% CI −0.43, −0.10] mmol/L; *P* = 0.001 [95% PI −0.89, 0.35 mmol/L]; *n* = 1,014 in 17 studies) (Fig. 2*B*) to a statistically significant but not clinically significant degree compared with control. Vitamin C had no statistically or clinically significant effects on LDL cholesterol (MD −0.23 [95% CI −0.48, 0.03] mmol/L; *P* = 0.08 [95% PI −1.25, 0.79 mmol/L]; *n* = 988 in 16 studies) (Fig. 2*C*), although it increased HDL cholesterol to a clinically important but not statistically significant degree (MD 0.06 [95% CI 0.00, 0.13] mmol/L; *P* = 0.06 [95% PI −0.17, 0.29 mmol/L]; *n* = 1,022 in 17 studies) (Fig. 2*D*) compared with control.

Three markers of lipid oxidation (malondialdehyde [MDA], F_2-isoprostanes, and LDL oxidation) were measured across more than one study and were included in meta-analyses. Vitamin C supplementation decreased plasma MDA to a statistically significant degree (standardized MD −1.25 [95% CI −1.88, −0.62]; *P* = 0.0001 [95% PI −3.44, 0.94]; *n* = 220 in five studies) but had no significant effects on F_2-isoprostanes or LDL oxidation compared with control (Supplementary Fig. 3). A study that measured susceptibility of LDL to oxidation that was not included in the analysis (28) reported no effect of vitamin C supplementation on this outcome. Another study found significantly lower plasma superoxide with vitamin C supplementation compared with placebo after 4 months (6). Also, skeletal muscle 2,7-dichlorodihydrofluorescein oxidation was found to decrease during insulin-stimulated conditions with vitamin C supplementation (42), although no

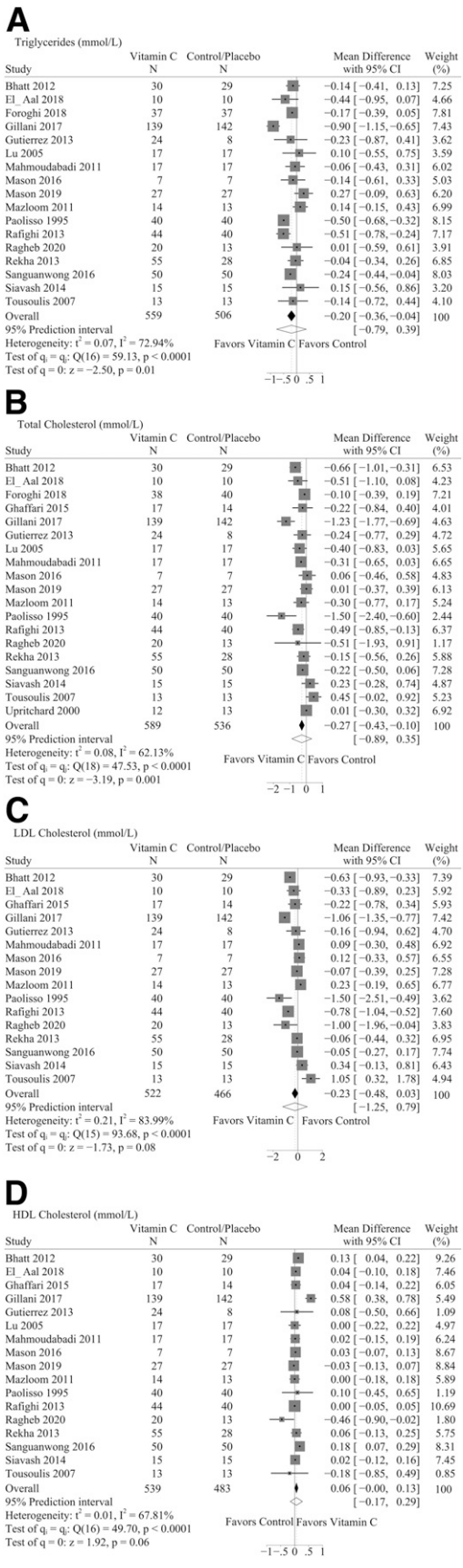

Figure 2—Forest plots of effect of vitamin C supplementation on primary lipid outcomes in people with type 2 diabetes. Effects on triglycerides (*A*), total cholesterol (*B*), LDL cholesterol (*C*), and HDL cholesterol (*D*).

change in whole-blood or skeletal muscle glutathione/glutathione disulfide ratio was found in that study.

Study heterogeneity was significant ($I^2 > 50\%$) for all glycemic control and lipid outcomes, DBP, and MDA, although not for other outcomes. Subgroup and meta-regression analyses of potentially modifying factors revealed that the most prominent effects on heterogeneity and efficacy were due to study sample size, study duration, and baseline HbA_{1c} (Supplementary Tables 3 and 4). Residual heterogeneity decreased below $I^2 = 50\%$ for HbA_{1c}, triglycerides, total cholesterol, and HDL cholesterol when the modifying factor was sample size in meta-regression analyses (Supplementary Table 4). With each increase of one participant per study, vitamin C significantly improved HbA_{1c} (−0.009%), fasting glucose (−0.007 mmol/L), triglycerides (−0.003 mmol/L), total cholesterol (−0.004 mmol/L), LDL cholesterol (−0.004 mmol/L), and HDL cholesterol (0.002 mmol/L). With each increase of 1 day in study duration, vitamin C significantly improved HbA_{1c} (−0.006%), fasting glucose (−0.005 mmol/L), triglycerides (−0.003 mmol/L), total cholesterol (−0.003 mmol/L), LDL cholesterol (−0.004 mmol/L), and HDL cholesterol (0.002 mmol/L). Meta-regression also revealed some significant effects when the modifying factors were baseline HbA_{1c} and daily vitamin C dose. For every 1% increase in baseline HbA_{1c}, vitamin C significantly decreased HbA_{1c} (−0.47%), fasting glucose (−0.57 mmol/L), triglycerides (−0.18 mmol/L), total cholesterol (−0.32 mmol/L), and LDL cholesterol (−0.55 mmol/L). For every 100 mg/day increase in vitamin C dose, vitamin C increased fasting glucose (0.09 mmol/L) and LDL cholesterol (0.07 mmol/L). Baseline age, BMI, diabetes duration, and vitamin C concentration had no significant modifying effect on heterogeneity or efficacy with vitamin C supplementation in subgroup or meta-regression analyses for any outcome except HDL cholesterol, which decreased with increasing baseline age (−0.01 mmol/L per 1-year increase) and increasing baseline BMI (−0.04 mmol/L per 1 kg/m^2 BMI increase). The number of low-risk-of-bias domains in studies were not found to significantly modify the efficacy and heterogeneity findings in either subgroup or meta-regression analyses.

Sensitivity analyses that were based on individual Cochrane risk-of-bias domains

Table 2—Summary of primary glycemic and cardiovascular risk factor outcomes with vitamin C supplementation

Outcome	Anticipated absolute effects* (95% CI)	Participants (RCTs), *n*	Certainty of the evidence (GRADE)	Minimal clinically important difference	Comments
HbA_{1c} (%)	MD 0.54 lower (0.90 lower to 0.17 lower)	1,133 (16)	⊕○○○ Very low†‡§‖	≥0.5	Vitamin C supplementation may improve HbA_{1c} to a clinically meaningful extent. Evidence rated down for inconsistency (1 level), imprecision (1 level), and indirectness (1 level). Subgroup and meta-regression analyses suggest the largest improvements with *1*) higher baseline HbA_{1c}, *2*) a longer supplementation duration, and *3*) larger study sample sizes.
Fasting glucose (mmol/L)	MD 0.74 lower (1.17 lower to 0.31 lower)	1,305 (20)	⊕○○○ Very low‡§‖	≥1	Evidence shows a statistically significant but clinically insignificant reduction in fasting glucose. Evidence rated down for risk of bias (1 level), inconsistency (1 level), imprecision (1 level), and indirectness (1 level). Subgroup and meta-regression analyses suggest the largest improvements with *1*) higher baseline HbA_{1c}, *2*) a longer supplementation duration, *3*) larger study sample sizes, and *4*) lower vitamin C supplementation doses.
SBP (mmHg)	MD 6.27 lower (9.6 lower to 2.95 lower)	466 (8)	⊕⊕⊕○ Moderate§#	>2	Evidence is suggestive of a hypotensive effect of vitamin C, with significant reductions observed that are consistent with a clinical improvement. Evidence rated down for indirectness (1 level).
DBP (mmHg)	MD 3.77 lower (6.13 lower to 1.42 lower)	466 (8)	⊕○○○ Very low‡§‖	>2	Evidence is suggestive of a hypotensive effect of vitamin C, with significant reductions observed that are consistent with a clinical improvement. Evidence rated down for inconsistency (1 level), imprecision (1 level), and indirectness (1 level).
Triglycerides (mmol/L)	MD 0.2 lower (0.36 lower to 0.04 lower)	1,065 (17)	⊕○○○ Very low‡§**	≥1	Evidence shows a small statistically significant but clinically insignificant reduction in triglycerides with vitamin C. Evidence rated down for risk of bias (1 level), inconsistency (1 level), imprecision (1 level), and indirectness (1 level). Subgroup and meta-regression analyses suggest the largest improvements with *1*) higher baseline HbA_{1c}, *2*) a longer supplementation duration, and *3*) larger study sample sizes.

Continued on p. 626

Table 2—Continued

Outcome	Anticipated absolute effects* (95% CI)	Participants (RCTs), *n*	Certainty of the evidence (GRADE)	Minimal clinically important difference	Comments
Total cholesterol (mmol/L)	MD 0.27 lower (0.43 lower to 0.1 lower)	1,125 (19)	⊕○○○ Very low‡§**	≥1	Evidence shows a small significant but clinically insignificant reduction in total cholesterol with vitamin C. Evidence rated down for risk of bias (1 level), inconsistency (1 level), imprecision (1 level), and indirectness (1 level). Subgroup and meta-regression analyses suggest the largest improvements with *1*) higher baseline HbA_{1c}, *2*) a longer supplementation duration, and *3*) larger study sample sizes.
LDL cholesterol (mmol/L)	MD 0.23 lower (0.48 lower to 0.03 higher)	988 (16)	⊕○○○ Very low‡§**	≥0.3	Overall, evidence is not supportive of a statistically or clinically significant reduction in LDL cholesterol with vitamin C. Evidence rated down for inconsistency (1 level), imprecision (1 level), and indirectness (1 level). Subgroup and meta-regression analyses suggest the largest improvements with *1*) higher baseline HbA_{1c}, *2*) a longer supplementation duration, *3*) larger study sample sizes, and *4*) lower vitamin C supplementation doses.
HDL cholesterol (mmol/L)	MD 0.06 higher (0.00–0.13 higher)	1,022 (17)	⊕○○○ Very low‡§‖	≥0.03	Overall, evidence is not supportive of a statistically significant change in HDL cholesterol with vitamin C, although mean changes found are potentially clinically meaningful. Evidence rated down for risk of bias (1 level), inconsistency (1 level), imprecision (1 level), and indirectness (1 level). Subgroup and meta-regression analyses suggest the largest improvements with *1*) a lower baseline BMI, *2*) a lower adult age, *3*) a longer study duration, and *4*) larger sample sizes.

*The risk in the intervention group and its 95% CI are based on the assumed risk in the comparison group and the relative effect of the intervention and its 95% CI). †Overall, findings alternated from significantly favoring vitamin C (5 domains) to borderline ($P = 0.05$) significant effects (2 domains) when undertaking sensitivity analyses on the basis of different individual Cochrane risk-of-bias domains when using only low-risk studies; a decision was made to not rate down for risk of bias because of this relative consistency. ‡Significant heterogeneity in meta-analysis ($I^2 > 50\%$). §Surrogate outcome measure, not a patient-important end point. ‖Upper bound 95% CI of estimate outside of clinical meaningfulness. Overall findings alternated from significantly favoring vitamin C to null effects when undertaking sensitivity analyses on the basis of different individual Cochrane risk-of-bias domains when using only low-risk studies. #Overall findings alternated from significantly favoring vitamin C to null effects when undertaking sensitivity analyses on the basis of different individual Cochrane risk-of-bias domains ($P < 0.05$ for all domains except for allocation concealment [$P = 0.06$] and blinding of outcome assessment [$P = 0.06$]) when using only low-risk-of-bias studies; a decision was made to not rate down for risk of bias because of this relative consistency. **Upper and/or lower bounds of 95% CI not clinically meaningful. |Lower bound 95% CI of estimate outside of clinical meaningfulness.

found mostly consistent significant effects favoring vitamin C when considering only low-risk-of-bias studies for DBP, MDA, HbA_{1c}, and SBP (Supplementary Table 2). Other measures either did not significantly favor vitamin C across most bias domains (LDL cholesterol, HDL cholesterol, F_2-isoprostanes, LDL oxidation, clamp insulin sensitivity, HOMA-IR) or produced statistically mixed results across individual bias domains (fasting glucose, fasting insulin, triglycerides, total cholesterol) when considering only low-risk-of-bias studies (Supplementary Table 2). There were no statistically significant small study effects found that were suggestive of publication bias (40) (Supplementary Fig. 4).

Table 2 presents a summary of findings with GRADE evidence for primary outcomes, and Supplementary Table 5 shows GRADE evidence profiles for these outcomes. SBP was found to have a moderate certainty of decreasing statistically and clinically with vitamin C supplementation. HbA_{1c} and DBP were found to have a very low certainty of decreasing statistically and clinically with vitamin C supplementation. Fasting glucose, triglycerides, total cholesterol, LDL cholesterol, and HDL cholesterol were evaluated as having very low evidence certainty, whether changes with vitamin C were statistically significant or not.

Adverse effects reporting was included in 13 studies (5,6,18,20,21,41,42,46–51) (Supplementary Table 6). Five studies (6,20,41,46,49) reported no adverse effects of supplementation without specifying actual outcomes assessed. One study (42) reported temporary gastrointestinal upset in one participant with vitamin C, while another study (5) mentioned a feeling of depression in one participant with placebo supplementation. Another study (21) reported no significant difference between vitamin C and control groups for symptoms including nausea, vomiting, diarrhea, giddiness, headache, oral mucosal erosion, and fatigue, although the number of affected individuals was not specified. Foroghi et al. (48) noted that 15% of participants in the vitamin C treatment group complained of physical discomfort, with no reports in the placebo group. Ragheb et al. (51) found significantly better quality-of-life survey scores following vitamin C supplementation in relation to role limitation to physical health and emotional problems compared with control. The most comprehensive reporting of adverse effects was documented in the study of Gillani et al. (18) in which significantly fewer adverse events were reported with vitamin C supplementation ($n = 23$, including two hypoglycemic episodes, three hyperglycemic episodes, and five wrong timing of medication intake) compared with placebo ($n = 89$, including 30 hypoglycemic episodes, 45 hyperglycemic episodes, and 11 wrong timing of medication). Finally, renal and hepatic function tests were conducted in several studies (5,6,18,41,42,50), which found no significant differences in outcomes between vitamin C and control groups.

CONCLUSIONS

The major findings of this review are that vitamin C supplementation significantly lowers HbA_{1c}, fasting and postprandial glucose, triglycerides, total cholesterol, SBP and DBP, and MDA in people with type 2 diabetes. However, because of study biases, heterogeneity between studies, indirectness of outcomes, and imprecision of findings, evidence certainty is mostly very low across these measures. The 95% PI included zero for most significant outcomes. This means that while on average vitamin C might have beneficial effects, it might not always be beneficial in an individual (i.e., clinical, study) setting. A notable limitation of studies included was that they were predominantly short term (<6 months) with a relatively small participant number ($n < 100$). Interestingly, the only study that was >6 months and with >250 participants yielded the largest improvements in glycemic control, lipids, and BP (18). Therefore, this review highlights that vitamin C supplementation may be beneficial for improving glycemic control and reducing risk factors associated with cardiovascular disease in type 2 diabetes. However, further investigations using larger sample sizes and longer supplementation periods are required to confirm these potential cardiometabolic benefits.

The mean magnitude of change in HbA_{1c} across studies is consistent with a clinical improvement (−0.54%). In contrast, a prior systematic review found no significant effect of vitamin C supplementation on HbA_{1c} in a subgroup analysis of people with type 2 diabetes (−0.15%) (8). We also found a larger effect size for fasting glucose than did that prior review (−0.74 vs. −0.44 mmol/L) (8). Notably, our review contained 10 additional studies ($n = 812$) for these outcomes that were published since that prior review. For glycemic control outcomes, subgroup analyses revealed greater effects of vitamin C when study duration was ≥12 weeks. Meta-regression analyses found that factors of increasing baseline HbA_{1c}, increasing study duration, and increasing sample size were potential modifying factors in terms of treatment efficacy. Thus, vitamin C might have greater effects on glycemic control when taken long term and for patients with higher HbA_{1c} levels.

Potential antihyperglycemic mechanisms of vitamin C action have not been well established but might plausibly include antioxidant effects of vitamin C that promote improved insulin sensitivity (5,6). However, direct evidence is scant and weak to support this effect in people with type 2 diabetes, with no significant effects and very low evidence certainty found for effects of vitamin C supplementation on clamp insulin sensitivity and HOMA-IR in our review.

The mean decreases in SBP (−6.27 mmHg) and DBP (−3.77 mmHg) were consistent with clinically meaningful improvements. These findings lend support to a prior systematic review (10) that found improvements in both SBP (−4.71 mmHg) and DBP (−4.07 mmHg) with vitamin C in a subgroup analysis in people with type 2 diabetes. However, that review included studies with concomitant intake of other antioxidant compounds along with vitamin C, thus limiting conclusions about vitamin C specifically. Given the moderate level of evidence certainty for SBP findings, it is possible that one of the strongest beneficial effects of vitamin C supplementation in people with type 2 diabetes is a reduction in BP.

Potential hypotensive mechanisms of vitamin C might relate to its potential to enhance nitric oxide (NO) synthesis and bioavailability through its antioxidant actions. Vitamin C is believed to scavenge superoxide (52) and, therefore, may decrease NO reactivity with superoxide and limit formation of the potential vasculature-damaging reactive species peroxynitrite. Vitamin C has also been shown to preserve concentrations of the endothelial NO synthase cofactor tetrahydrobiopterin, in turn maintaining NO production through endothelial NO synthase (53).

The significant improvements for triglycerides (−0.2 mmol/L) and total cholesterol (−0.27 mmol/L) observed are arguably not of clinical significance. These findings partially support subgroup analyses in people with type 2 diabetes in a previous systematic review that similarly reported a statistically significant decrease in triglycerides (−0.15 mmol/L) with vitamin C supplementation (9). Despite small effect sizes for lipid outcomes overall, effects were larger for most lipid outcomes in subgroup analyses when study duration was ≥12 weeks and vitamin C dose was <1,000 mg/day. Meta-regression analyses found that factors of increasing baseline HbA_{1c}, increasing study duration, and increasing sample size were potential modifying

factors in terms of treatment efficacy on lipid outcomes. Findings of increased efficacy with lower vitamin C doses implies an upper dose limit of effectiveness of vitamin C. However, it should be noted that there were only four studies in the review that used doses >1,000-mg/day and only two studies that used a dose of <500 mg/day. Thus, beneficial lipid-related effects may be most evident when modest doses are taken long term and for patients with higher HbA_{1c}.

We found significant effects of vitamin C supplementation on plasma MDA. A prior systematic review found significant effects of vitamin supplementation on MDA in people with type 2 diabetes (12). However, that review was not specific to vitamin C. Evidence for effects of vitamin C as a single-compound supplement on MDA is limited to a small number of studies and has significant between-study heterogeneity. Studies have shown vitamin C to be an effective antioxidant at reducing lipid peroxidation in human plasma (54,55). However, given current low-quality evidence in people with type 2 diabetes, further studies are required to evaluate effects of vitamin C on lipid peroxidation and other oxidative stress markers in type 2 diabetes.

A limitation of this review was a failure to extract relevant data from four studies (15–18) that may have been included in the analyses of lipids and BP. However, it is unlikely that inclusion of these studies would have decreased the effect sizes observed because abstract (15) and results (18) data from these studies have suggested significant improvements with vitamin C supplementation. Also, while we reported few notable adverse effects in studies, our review did not involve a comprehensive search of adverse effects. More focused reviews of adverse effects of vitamin C supplementation in people with type 2 diabetes are required.

Studies included in the review did not include patient-important outcomes, such as diabetic complications, cardiovascular disease incidence, or mortality. The lack of evidence on these outcomes in RCTs with vitamin C supplementation in people with type 2 diabetes is a gap in the literature that requires further investigation.

While we did include exploratory subgroup and meta-regression analyses of outcomes on the basis of plasma vitamin C status, most studies included in the review did not measure participants' vitamin C concentrations. Therefore, it remains unclear whether baseline vitamin C status might affect the outcomes explored in our review. Finally, most studies included in the review involved the concomitant use of diabetes treatments, and some studies allowed BP- and lipid-lowering medications. Therefore, we cannot draw any clear conclusions about the efficacy of vitamin C as a standalone therapeutic agent for diabetes management but more so as an add-on therapy to existing diabetic therapies.

Vitamin C supplements are relatively inexpensive and widely available. Thus, vitamin C might be a potentially cost-effective treatment for people with type 2 diabetes. However, there is currently a lack of investigation of the cost-effectiveness of this approach. Thus, further investigation is required to evaluate the potential cost-effectiveness of vitamin C supplementation for the management of people with type 2 diabetes.

While our study only investigated effects of supplemental vitamin C on outcomes, it is possible that regular high dietary intakes of vitamin C could yield similar outcomes for people with type 2 diabetes, although there is a paucity of well-controlled studies in this area. Furthermore, foods rich in vitamin C may also be rich in additional nutrients, like vitamins, minerals, phytonutrients, and dietary fiber, that may have additional beneficial effects for people with diabetes. Future research should address effects of vitamin C supplements versus other antioxidant compounds or antioxidant-rich diets to establish whether the effects are specific to vitamin C or are more general with regard to vitamin C as an antioxidant.

Our findings, which are based largely on short-term studies with low evidence quality, suggest that vitamin C supplementation may be potentially effective for improving glycemic control and BP in people with type 2 diabetes. These effects may be greatest in people with higher HbA_{1c} and in those who regularly supplement with vitamin C. However, given limitations of studies, vitamin C supplementation cannot currently be recommended for type 2 diabetes management, with further investigations using larger sample sizes and longer supplementation periods that are powered to stratify effects on the basis of baseline glycemic control required to confirm beneficial effects of vitamin C supplementation.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.
Author Contributions. S.A.M. and G.D.W. conceived the study. S.A.M. and G.D.W. extracted and reviewed the data independently, and M.A.K. resolved any discrepancies. S.A.M. and G.D.W. performed the statistical analyses. S.A.M., G.D.W., and M.A.K. interpreted the data. S.A.M. wrote the manuscript with input from G.D.W. and M.A.K.

References

1. American Diabetes Association. 10. Cardiovascular disease and risk management: *Standards of Medical Care in Diabetes—2020*. Diabetes Care 2020;43(Suppl. 1):S111–S134
2. Houstis N, Rosen ED, Lander ES. Reactive oxygen species have a causal role in multiple forms of insulin resistance. Nature 2006;440:944–948
3. Brownlee M. Biochemistry and molecular cell biology of diabetic complications. Nature 2001;414:813–820
4. Hodaei H, Adibian M, Nikpayam O, Hedayati M, Sohrab G. The effect of curcumin supplementation on anthropometric indices, insulin resistance and oxidative stress in patients with type 2 diabetes: a randomized, double-blind clinical trial. Diabetol Metab Syndr 2019;11:41
5. Mason SA, Rasmussen B, van Loon LJC, 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 Metab 2019;21:674–682
6. 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;14:387–392
7. Seyyedebrahimi S, Khodabandehloo H, Nasli Esfahani E, Meshkani R. The effects of resveratrol on markers of oxidative stress in patients with type 2 diabetes: a randomized, double-blind, placebo-controlled clinical trial. Acta Diabetol 2018;55:341–353
8. Ashor AW, Werner AD, Lara J, Willis ND, Mathers JC, Siervo M. Effects of vitamin C supplementation on glycaemic control: a systematic review and meta-analysis of randomised controlled trials. Eur J Clin Nutr 2017;71:1371–1380
9. Ashor AW, Siervo M, van der Velde F, Willis ND, Mathers JC. Systematic review and meta-analysis of randomised controlled trials testing the effects of vitamin C supplementation on blood lipids. Clin Nutr 2016;35:626–637
10. Juraschek SP, Guallar E, Appel LJ, Miller ER III. Effects of vitamin C supplementation on blood pressure: a meta-analysis of randomized controlled trials. Am J Clin Nutr 2012;95:1079–1088
11. Ashor AW, Lara J, Mathers JC, Siervo M. Effect of vitamin C on endothelial function in health and disease: a systematic review and meta-analysis of randomised controlled trials. Atherosclerosis 2014;235:9–20

12. Balbi ME, Tonin FS, Mendes AM, et al. Antioxidant effects of vitamins in type 2 diabetes: a meta-analysis of randomized controlled trials. Diabetol Metab Syndr 2018;10:18
13. Akbar S, Bellary S, Griffiths HR. Dietary antioxidant interventions in type 2 diabetes patients: a meta-analysis. Br J Diabetes Vasc Dis 2011;11:62–68
14. Tabatabaei-Malazy O, Nikfar S, Larijani B, Abdollahi M. Influence of ascorbic acid supplementation on type 2 diabetes mellitus in observational and randomized controlled trials; a systematic review with meta-analysis. J Pharm Abdullahi Sci 2014;17:554–582
15. Chaudhari H, Dakhale G, Chaudhari S, Kolhe S, Hiware S, Mahatme M. The beneficial effect of vitamin C supplementation on serum lipids in type 2 diabetic patients: a randomized double blind study. Int J Diabetes Metab 2012; 20:53–58
16. Gupta P, Goyal RK, Maheshwari S, Kaushik GG. Effect of antioxidant therapy on serum superoxide dismutase activity in patients with type-2 diabetes mellitus. J Assoc Physicians India 2000;48:756–757
17. Mahmoudabadi MM, 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 2011;16(Suppl. 1):S361–S367
18. 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;16:103
19. Higgins JP, Altman DG, Gøtzsche PC, et al.; Cochrane Bias Methods Group; Cochrane Statistical Methods Group. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928
20. 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. Int J Toxicol Pharmacol Res 2016;8: 114–119
21. Rekha NMR, Sattigeri B. Comparison of efficacy and tolerability of vitamin C as add on therapy to the oral hypoglycaemic agent in newly diagnosed type 2 diabetes mellitus. Int J Drug Dev Res 2013;5:187–194
22. Gutierrez AD, Duran-Valdez E, Robinson I, de Serna DG, Schade DS. Does short-term vitamin C reduce cardiovascular risk in type 2 diabetes? Endocr Pract 2013;19:785–791
23. Tessier DM, Khalil A, Trottier L, Fülöp T. Effects of vitamin C supplementation on antioxidants and lipid peroxidation markers in elderly subjects with type 2 diabetes. Arch Gerontol Geriatr 2009;48:67–72
24. Higgins JP, Thomas J, Chandler J, et al. *Cochrane Handbook for Systematic Reviews of Interventions*. Chichester, U.K., John Wiley & Sons, 2019
25. Mullan BA, Young IS, Fee H, McCance DR. Ascorbic acid reduces blood pressure and arterial stiffness in type 2 diabetes. Hypertension 2002; 40:804–809
26. Shateri Z, Keshavarz S, Hosseini S, Chamari M, Hosseini M, Nasli E. Effect of vitamin C supplementation on blood pressure level in type 2 diabetes mellitus: a randomized, double-blind, placebo-controlled trial. Biosci Biotechnol Res Asia 2016;13:279–286
27. Darko D, Dornhorst A, Kelly FJ, Ritter JM, Chowienczyk PJ. Lack of effect of oral vitamin C on blood pressure, oxidative stress and endothelial function in Type II diabetes. Clin Sci (Lond) 2002; 103:339–344
28. Upritchard JE, Sutherland WH, Mann JI. Effect of supplementation with tomato juice, vitamin E, and vitamin C on LDL oxidation and products of inflammatory activity in type 2 diabetes. Diabetes Care 2000;23: 733–738
29. Cochrane. Review Manager (RevMan) 5.3 [Computer program]. Copenhagen, The Nordic Cochrane Centre, The Cochrane Collaboration, 2014
30. Riley RD, Higgins JPT, Deeks JJ. Interpretation of random effects meta-analyses. BMJ 2011;342: d549
31. McMaster University. GRADEpro GDT. GRADEpro Guideline Development Tool. Hamilton, Ontario, Canada, Evidence Prime, 2015
32. Balshem H, Helfand M, Schünemann HJ, et al. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol 2011;64:401–406
33. Lenters-Westra E, Schindhelm RK, Bilo HJ, Groenier KH, Slingerland RJ. Differences in interpretation of haemoglobin A1c values among diabetes care professionals. Neth J Med 2014;72: 462–466
34. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33) [published correction appears in Lancet 1999;354: 602]. Lancet 1998;352:837–853
35. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). JAMA 2001;285: 2486–2497
36. Rahilly-Tierney CR, Lawler EV, Scranton RE, Gaziano JM. Cardiovascular benefit of magnitude of low-density lipoprotein cholesterol reduction: a comparison of subgroups by age. Circulation 2009;120:1491–1497
37. Gordon DJ, Probstfield JL, Garrison RJ, et al. High-density lipoprotein cholesterol and cardiovascular disease. Four prospective American studies. Circulation 1989;79:8–15
38. Stamler J. The INTERSALT study: background, methods, findings, and implications. Am J Clin Nutr 1997;65(Suppl.):626S–642S
39. Guyatt GH, Oxman AD, Kunz R, et al.; GRADE Working Group. GRADE guidelines: 8. Rating the quality of evidence–indirectness. J Clin Epidemiol 2011;64:1303–1310
40. Sterne JA, Gavaghan D, Egger M. Publication and related bias in meta-analysis: power of statistical tests and prevalence in the literature. J Clin Epidemiol 2000;53:1119–1129
41. 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. Adv Pharmacol Sci 2011; 2011:195271
42. 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;93:227–238
43. 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 (Lond) 2005;108: 507–513
44. 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:H137–H145
45. Mahmoudabadi MM, Rahbar AR. Effect of EPA and vitamin C on superoxide dismutase, glutathione peroxidase, total antioxidant capacity and malondialdehyde in type 2 diabetic patients. Oman Med J 2014;29:39–45
46. 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 Dent 2019;13:444–449
47. 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: 77–82
48. Foroghi M, Ghatre Samani K, Heidarian E, Nikokar M, Fazeli S. Study effects of resveratrol, cuminumcyminum, essence and vitamin C on blood sugar, lipid, insulin resistance and advanced glycated end products (AGEs) in type 2 diabetic patients. Iran J Endocrinol Metab 2018; 20:169–176
49. Devanandan P, Chowdary RP, Muthukumar VA. Effects of vitamin C supplementation on the glycemic control and cardiovascular risk in type II diabetes mellitus. J Res Pharm 2020; 24:182–187
50. El-Aal AA, El-Ghffar EAA, 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 Metab Syndr 2018;12:483–489
51. 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. Clin Nutr ESPEN 2020;35: 128–135
52. 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;47:1–7
53. Huang A, Vita JA, Venema RC, Keaney JF Jr. Ascorbic acid enhances endothelial nitric-oxide synthase activity by increasing intracellular tetrahydrobiopterin. J Biol Chem 2000;275:17399–17406
54. Frei B, England L, Ames BN. Ascorbate is an outstanding antioxidant in human blood

plasma. Proc Natl Acad Sci U S A 1989;86:6377–6381
55. Polidori MC, Mecocci P, Levine M, Frei B. Short-term and long-term vitamin C supplementation in humans dose-dependently increases the resistance of plasma to ex vivo lipid peroxidation. Arch Biochem Biophys 2004;423:109–115
56. Bhatt JK, Thomas S, Nanjan MJ. Effect of oral supplementation of vitamin C on glycemic control and lipid profile in patients with type 2 diabetes mellitus. Int J Pharm Nanjing Sci 2012;4:524–527
57. Ghaffari P, Mehdi N, Gharib A, Rahimi F. The effects of vitamin C on diabetic patients. Der Pharm Lett 2015;7:68–71
58. Mazloom Z, Hejazi N, Dabbaghmanesh MH, Tabatabaei HR, Ahmadi A, Ansar H. Effect of vitamin C supplementation on postprandial oxidative stress and lipid profile in type 2 diabetic patients. Pak J Biol Sci 2011;14:900–904
59. Rafighi Z, Shiva A, Arab S, Mohd Yousof R. Association of dietary vitamin C and e intake and antioxidant enzymes in type 2 diabetes mellitus patients. Glob J Health Sci 2013;5:183–187
60. Tousoulis D, Antoniades C, Vasiliadou C, et al. Effects of atorvastatin and vitamin C on forearm hyperaemic blood flow, asymmetrical dimethylarginine levels and the inflammatory process in patients with type 2 diabetes mellitus. Heart 2007;93:244–246