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Does vitamin C supplementation exert profitable effects on serum lipid profile in patients with type 2 diabetes? A systematic review and meta-analysis

Zahra Namkhah¹, Damoon Ashtary-Larky², Fatemeh Naeini¹, Cain C. T. Clark³, Omid Asbaghi³

¹Department of Clinical Nutrition, School of Nutritional Sciences and Dietetics, Tehran university of medical science, Tehran, Iran

²Nutrition and Metabolic Diseases Research Center, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran

³Centre for Intelligent Healthcare, Coventry University, Coventry, CV1 5FB, U.K.

⁴Student Research Committee, Lorestan University of Medical Sciences, Khorramabad, Iran

Abstract

Introduction: Previous studies have reported that vitamin C supplementation may decrease lipid profile in patients with type 2 diabetes mellitus (T2DM). This systematic review and meta-analysis evaluated the influence of vitamin C supplementation on lipid profile in patients with T2DM.

Methods: Studies examining the effects of vitamin C supplementation on lipid profile in patients with T2DM, published up to November 2020, were identified through PubMed, SCOPUS, and Embase databases. 15 studies, including 872 participants, were included and analyzed using a random-effects model to calculate weighted mean differences (WMDs) with 95% confidence intervals (CI).

Results: Findings from 15 studies indicated that vitamin C supplementation significantly decreased Triglyceride (TG) (WMD: -16.48 mg/dl, 95% CI (-31.89, -1.08), $P < 0.001$) and total cholesterol (TC) (WMD: -13.00 mg/dl, 95% CI (-23.10, -2.91), $P < 0.001$) in patients with T2DM. However, vitamin C supplementation failed to improve LDL and HDL. The meta-regression analysis suggested that lipid profile improvement was affected by duration of vitamin C treatment. Dose-response analysis showed that vitamin C supplementation changed LDL significantly based on vitamin C dose.

Conclusion: According to our findings, vitamin C supplementation significantly improved lipid profile via decreases in TG and TC. However, vitamin C failed to affect LDL and HDL in diabetic populations. It appears that vitamin C supplementation is more beneficial to lipid profile in long-term vs. short term interventions.

Keywords: lipid profile, dyslipidemia; diabetes; vitamin C; meta-analysis.

1. Introduction:

One of the most important metabolic disorders associated with high blood glucose concentrations due to dysfunction in insulin secretion, insulin action, or both, is diabetes mellitus (DM) (1, 2). In 2019, 9.3% of the adult population, worldwide (463 million), were estimated to be living with

diabetes, and this number is estimated to surge to 700 million by 2045 (3). As a result of such high prevalence, people with insulin resistance will propagate multiple cardiovascular risk factors, including hypertension, chronic kidney disease, microalbuminuria, and dyslipidemia (4). Diabetic dyslipidemia is a cluster of lipoprotein abnormalities, consisting of elevated triglyceride levels, decreased high-density lipoprotein (HDL) cholesterol concentrations, and a preponderance of small-dense low-density lipoprotein (LDL) particles (5-7). Given that nearly 66% of deaths in people with DM can be attributed to cardiovascular disease (CVD), it is necessary to effectively manage and control diabetes (8). There are demonstrable links among key modifiable diabetes risk factors, including genetic, aging process, environmental factors, and lifestyle (9). Indeed, lifestyle factors, including inactivity and diet, have profound effects on the occurrence of type 2 diabetes mellitus (T2DM), which accounts for around 90% of all diabetic cases (2). Some empirical evidence has highlighted the role of free radical in the pathogenesis of DM; the body has several endogenous antioxidant systems to manage the detrimental effects of reactive species. Moreover, obtaining exogenous antioxidants from the diet has been shown to neutralize reactive oxygen species and contribute to the body homeostasis (10, 11).

Ascorbic acid (L-ascorbic acid or ascorbate), generally known as vitamin C, is a water-soluble non-enzymatic antioxidant that scavenges reactive oxygen and nitrogen species (RONS) and reduces oxidative stress *in vivo* and *in vitro* (12, 13). Vitamin C is not synthesized in the human body and, therefore, diet is considered as the main source (12). Lower concentrations of ascorbic acid in diabetic patients has been reported to lead to increased oxidative stress (14, 15). Moreover, fasting plasma glucose (FPG) levels have been negatively associated with vitamin C intake (16, 17). Vitamin C is involved in the regulation of cholesterol catabolism to bile acids and has been posited to be the main factor in lipid modulation (18). Indeed, via conversion of cholesterol to bile acids, and increases in the LDL receptors on hepatocytes, cholesterol uptake from the circulation may be elevated and lead to a reduction in LDL concentrations in the blood (19). Moreover, via its' antioxidative effects, vitamin C prohibits the oxidation of LDL and facilitates its uptake through LDL receptors on hepatocytes (20). Indeed, a clinical trial showed that high doses of vitamin C improved blood glucose regulation and reduced serum levels of triglyceride and cholesterol in type 2 diabetic patients (18). In another study, by Paolisso et al (21), on patients with type 2 diabetes, supplementation with 500 mg vitamin C significantly reduced the plasma levels of LDL, TC, TG, and insulin. Contrastingly, however, Siavash et al (22) observed that administration of 1000mg vitamin C, for six weeks, did not significantly decrease serum TG and TC concentrations.

Given the current lack of consensus, we performed a systematic review and meta-analysis of published trials to evaluate the effects of vitamin C supplementation on serum lipid profile in type 2 diabetic patients. Indeed, to our knowledge, no meta-analysis has been conducted in this regard.

2. Methods:

This systematic review and meta-analysis was performed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (23).

2.1.Literature Search strategy

PubMed (<http://www.ncbi.nlm.nih.gov/pubmed>), Scopus (<http://www.scopus.com>), and Embase were searched, by two independent researchers, from database inception up to November 2020. Medical subject headings (MeSH) and non-MESH search terms included: (("vitamin C" OR "ascorbic acid" OR ascorbate) AND ("Type 2 diabetes" OR T2DM OR diabetes OR "gestational diabetes mellitus" OR GDM) AND (Intervention OR "controlled trial" OR randomized OR randomized OR random OR randomly OR placebo OR "clinical trial" OR Trial OR "randomized controlled trial" OR "randomized clinical trial" OR RCT OR blinded OR "double blind" OR "double blinded" OR trial OR "clinical trial" OR trials OR "Cross-Over" OR parallel)). Moreover, to avoid missing any related studies, we also manually searched the reference lists of the included papers.

2.2.Study selection

Firstly, two researchers (Z.N and F.N) ascertained eligible articles by reading titles, abstracts, and, if required, the full-text version of publications. We included all clinical controlled trials (either parallel or cross-over designs) examining the effect of vitamin C supplementation on lipid profile in patients with type 2 diabetes. Studies were excluded if they were: letters, comments, conference papers, reviews, meta-analysis, ecologic studies, RCTs without an appropriate control group, publications with duplicate data, and studies without sufficient data. Any conflict regarding to the study selection process was resolved by discussion with a third researcher (O.A).

2.3.Data extraction and management

The following data were collected from each study: basic characteristics (first author's last name, publication year, location of the study, study design, target population, age and gender of participants, total sample size, study duration, type of intervention in groups of study, the dose of vitamin C supplementation, duration of diabetes, body weight, body mass index) and main results (mean and Standard Deviation (SD) of lipid profile for both control and intervention groups at baseline, and end of study). Data extraction was conducted by two authors, independently (Z.N and O.A).

2.4.Quality assessment of studies

We used Cochrane criteria to assess the potential risk of bias and quality of studies (24). The salient elements of this tool include: random sequence generation, allocation concealment, blinding, incomplete outcome data, and other bias. According to the Cochrane Collaboration's tool, studies were classified as low, high, or unclear risk of bias regarding each section.

2.5. Statistical analysis

All statistical analyses were conducted using STATA software version 12 (STATA corp, College Station, TX, USA). For estimation of the effect size of vitamin C on serum lipid profile, the mean change and its standard deviation, in both intervention and control arms, were used. The SD of the mean difference for studies that not reported was calculated by the following formula: $S.D \text{ change} = \sqrt{[(S.D \text{ baseline})^2 + (S.D \text{ final})^2 - (2 \times R \times S.D \text{ baseline} \times S.D \text{ final})]}$ where correlation coefficient (R) was considered as 0.9. The fixed-effect (I squared < 50 %) or random-effect models (I squared > 50 %) were used to evaluate the weighted mean difference (WMD) with 95% confidence intervals (CI) (25). Possible publication bias was scrutinized using visual assessment of funnel plots and results of Begg's and Eggers' regression test. To recognize the source of heterogeneity among included studies, subgroup analysis based on baseline serum concentrations of lipid profile, intervention dosage (≥ 1000 mg and < 1000 mg) and duration (≥ 12 weeks and < 12 weeks) was conducted. A sensitivity analysis was performed, by removing each study one by one, to explore the contribution of each study to the overall mean difference. Statistical significance was as accepted, *a priori*, at $P < 0.05$.

3. Results:

3.1. Study selection

A total of 2365 articles were found through databases searching, 595 of which were duplicates. Among the remaining papers, 1747 records were eliminated due to the following reasons: reviews (n=76), animal studies (n=213), and unrelated titles and abstracts (n = 1458). 23 articles were selected for full-text assessment, an additional 8 studies were excluded because of not reporting lipid profile. Finally, 15 original articles (21, 22, 26-38) were included in this systematic review and meta-analysis (**Fig. 1**).

3.2. Study characteristics

Detailed characteristics of the evaluated trials are reported in **Table 1**. Of these, 15 trials, with 17 effect sizes (21, 22, 26-38), which were published between 1995 and 2019, were included. 8 studies were conducted in Asia (22, 29, 30, 32-35, 38), 4 in Europe (21, 26-28), 2 in Australia (31, 36), and 1 in Africa (37). All were parallel (n=11) and cross-over studies (n=4) (21, 27, 31, 36), and admitted 435 participants in the intervention group and 437 in the control group, respectively. The intervention period varied from 2 to 48 weeks, whilst supplementation dose of vitamin C ranged between 200 and 2000 mg/d. All of the included studies recruited both genders, however two studies were conducted on males only (29, 35). Baseline mean age and body mass index (BMI) varied from 36 to 72 years and 23.5 to 34 kg/m², respectively. Eligible studies were carried out on subjects with type 2 DM. The results of quality assessment of included studies based on the Cochrane Collaboration's tool are depicted in **Table 2**.

3.3.Effect of vitamin c on TG levels

In total, 15 eligible studies with 17 effect sizes, examined the effect of vitamin C intake on TG Level. This meta-analysis highlighted a significant decrease in TG levels (WMD: -16.48 mg/dl, 95% CI (-31.89, -1.08), $P = 0.036$; $I^2 = 84.2\%$, $P < 0.001$) (**Fig. 2**). After subgroup analysis, trial duration ≥ 12 weeks yielded a significant reduction in TG levels (WMD: -36.91 mg/dl, 95% CI (-58.78, -15.05), $P = 0.001$) (**Table 3**). Although meta-regression analysis showed a linear relationship between trial duration and TG concentrations ($P = 0.011$) (**Fig. 3**), dose-response analysis did not reveal any significant effect for dose ($P = 0.690$) or duration ($P = 0.660$) (**Fig. 4**).

3.4.Effect of vitamin c on TC levels

15 studies with 17 effect sizes reported the effects of vitamin C supplementation on TC levels. Overall, vitamin C supplementation significantly reduced TC (WMD: -13.00 mg/dl, 95% CI (-23.10, -2.91), $P = 0.012$; $I^2 = 87.2\%$, $P < 0.001$). Regarding subgroup analysis, reduction of TC levels was significant in participants who had baseline serum TC > 200 mg/dl (WMD: -24.46 mg/dl, 95% CI (-41.79, -7.14), $P = 0.006$), and when the trial duration was ≥ 12 (WMD: -27.63 mg/dl, 95% CI (-53.25, -2.00), $P = 0.035$). Meta-regression analysis demonstrated a significant relationship between trial duration and changes in TC ($P = 0.005$), but the significant association was not observed for dose ($P = 0.103$) and duration ($P = 0.095$).

3.5.Effect of vitamin c on LDL concentrations

Combining 15 effect sizes from the 13 studies did not reveal any significant effects of vitamin C administration on LDL concentrations (WMD: -7.54 mg/dl, 95% CI (-17.34, 2.26), $P = 0.132$; $I^2 = 87.3\%$, $P < 0.001$). However, across studies with duration time equal or higher to 12 weeks, LDL levels were significantly decreased (WMD: -19.72 mg/dl, 95% CI (-37.15, -2.29), $P = 0.027$), and, based on meta-regression analysis, there was a significant association between trial duration and the LDL levels ($P = 0.016$). Furthermore, dose-response analysis suggested that vitamin C intake significantly altered LDL levels based on treatment dose ($r = 41.8612$, $P = 0.022$).

3.6.Effect of vitamin c on HDL concentrations

The results (14 studies, 16 effect sizes) demonstrated that the pooled effect size was not significant (WMD: 2.21 mg/dl, 95% CI (-0.53, 4.95), $P = 0.115$; $I^2 = 81.6\%$, $P < 0.001$). While subgroup analysis, based on trial duration, showed non-significant effects of vitamin C on HDL levels in < 12 weeks (WMD: 0.47 mg/dl, 95% CI (-2.66, 3.60), $P = 0.768$), a borderline significant elevation was observed in studies with duration time equal or higher than 12 weeks (WMD: 4.51 mg/dl, 95% CI (-0.42, 9.45), $P = 0.073$). Meta-regression and dose-response analysis revealed that the effects of vitamin C supplementation on HDL levels had a positive association with trial duration ($P < 0.001$; $r = 0.094512$, $P = 0.040$, respectively).

3.7.Sensitivity analysis

Each study was omitted from the analysis to explore the impact of every individual trial on the overall effect size. Although, there was no significant effect of any single study on the pooled effect sizes of TC and HDL, sensitivity analysis for TG revealed that the exclusion of studies carried out by Paolisso et al. (21) (WMD: -14.33, 95% CI: -30.55, 1.89), Sanguanwong et al. (32) (WMD: -14.88, 95% CI: -31.35, 1.57), Hamed et al. (33) (WMD: -13.66, 95% CI: -29.32, 2.00), Gillani et al. (34) (WMD: -12.20, 95% CI: -25.58, 1.18), El-Aal et al. (35) (WMD: -15.19, 95% CI: -31.19, 0.81), and Foroughi et al. (38) (WMD: -16.45, 95% CI: -33.51, 0.60), respectively, altered the overall estimates. In addition, sensitivity analysis showed that the effect of vitamin C on the levels of LDL was significant after the exclusion of one clinical trial (28) (WMD: -10.162535 mg/dl, 95% CI, -19.730852, -.59421659).

3.8.Publication Bias

There was no detectable publication bias for TG ($p = 0.086$, Egger's test and $p = 0.902$, begg's test), TC ($P= 0.991$, Egger's test and $p = 0.434$, begg's test), LDL ($p = 0.863$, Egger's test and $p = 0.553$, begg's test), and HDL ($p = 0.644$, Egger's test and $p = 0.753$, begg's test) (**Fig. 5**).

4. Discussion

In this meta-analysis, we evaluated the effects of vitamin C supplementation on lipid profile in patients with T2DM. According to the results derived from this study, vitamin C supplementation significantly improved lipid profile by decreasing TG and TC. However, vitamin C failed to significantly alter LDL and HDP. According to our subgroup analysis on TG and TC, patients receiving vitamin C were more likely to benefit from long-term (≥ 12 weeks) vs short term (< 12 weeks) interventions. Moreover, vitamin C administration yielded significant decreases in TG when patients received the higher (> 200 mg/day) vs. Lower doses (≤ 200 mg). In terms of LDL, vitamin C supplementation significantly decreased serum LDL levels when administered for 12 weeks or more. Whilst for HDL, vitamin C supplementation failed to increase serum HDL levels among patients with T2DM. The meta-regression analysis suggested that lipid profile improvement was affected by duration of vitamin C treatment, and dose-response analysis indicated that vitamin C supplementation significantly altered LDL based on vitamin C dose.

Dyslipidemia is a common feature of DM (39, 40); indeed, it is a genetic and/or multifactorial disorder of lipoprotein metabolism that causes atherosclerosis and progressive cardiovascular problems, particularly in patients with T2DM (41-43). Previous epidemiological studies have reported that vitamin C deficiency, measured by dietary intake or plasma concentration of ascorbic acid, is associated with a higher risk of mortality from CVD (44-46). In terms of the effects of vitamin C supplementation on lipid profile, previous studies have reported equivocal results (47-49). In 2016, a meta-analysis revealed that vitamin C supplementation had no significant effect on

lipid profile (50); however, the authors reported a significant reduction in blood lipids following supplementation in sub-populations with dyslipidemia or low vitamin C status at baseline.

The mechanisms underlying the effects of vitamin C supplementation and lipid profile in patients with T2DM remains unclear. However, we posit five putative reasons for the apparent null relation between vitamin C supplementation and lipid profile in our meta-analysis. Firstly, the beneficial effect of vitamin C appears to emerge from the vitamins' antioxidant capabilities; indeed, increased oxidative stress appears to be a deleterious factor leading to dyslipidemia in patients with T2DM (51). Antioxidant supplementation can modulate lipid profile by improving oxidative stress (52). Second, proper control of glycemic profile in patients with T2DM may improve lipid profile (53, 54). Evidence from animal and human studies has suggested that oxidative stress can influence insulin secretion and glucose metabolism (55, 56). Given that previous studies have revealed that dietary total antioxidant capacity has a protective role in improving glycemic profile (57-59), it is plausible that vitamin C supplementation, as a dietary antioxidant, may play a role in improving dyslipidemia by controlling glycemic profile. Indeed, it seems that these benefits of vitamin C may be mediated by inhibition of lipid oxidation (60). Third, some evidence has suggested that the beneficial effects of vitamin C supplementation on lipid profile may be more effective in populations with dyslipidemia, compared to normolipidemic counterparts (50). Moreover, global statistics indicate that the prevalence of dyslipidemia in patients with T2DM is higher than healthy controls (61, 62). Since the participants of the most of included studies in our analysis were diabetic patients with dyslipidemia, the hypolipidemic benefits of vitamin C supplementation may be related to higher baseline lipid profile levels. Fourth, it is well-established that there is a higher risk of vitamin C deficiency among patients with T2DM (63, 64), where evidence has suggested that patients with T2DM have at least 30% lower circulating vitamin C than people without T2DM (65). Moreover, current data suggests that the hypolipidemic effects of vitamin C supplementation is more potent in subjects with low plasma vitamin C levels (50, 66). However, only four studies reported baseline levels of vitamin C levels in our analysis. These four studies were conducted on patients with inadequate (67) (< 28 micromole/L), marginal (21, 68) (<45 micromole/L) and adequate (69) (49-58 micromole/L) serum ascorbic acid levels. Therefore, it may be difficult to determine which studies investigate the effects of vitamin C in patients with vitamin C deficiency. Moreover, none of included studies reported dietary intake of vitamin C. Therefore, determining whether low vitamin intake influenced the results is infeasible. Fifth, vitamin C is involved in the regulation of cholesterol catabolism to bile acids, and it has been posited to be the main factor in lipid modulation (18). By converting cholesterol to bile acids and increasing the LDL receptors on hepatocytes, cholesterol uptake from the circulation may be elevated and, eventually, LDL concentrations can be decreased in the blood (19). In addition, the antioxidant power of vitamin C in diabetic patients can inhibit the oxidation of LDL from non-enzymatic glycosylation and peroxidation phenomena, and facilitates its uptake through LDL receptors on hepatocytes, thereby enhancing LDL catabolic pathway (20, 21). Future mechanistic studies are needed to evaluate the possible mechanisms underlying the effects of vitamin C supplementation and lipid profile in patients with T2DM

Given that 7 of the 15 trials in the present study lasted equal to or more than 12 weeks, an important strength of our analysis is our ability to indicate the long-term effects of vitamin C supplementation on lipid profile in patients with T2DM. However, some limitations of the analysis should be considered. There was a notable heterogeneity in the results of the studies included. Indeed, it seems that the heterogeneity is attributable to clinical baseline heterogeneity, including differences between sample characteristics of the studies, dissimilar dosages, and different study design types in the included studies. Moreover, most included studies did not report serum levels and dietary intake of vitamin C. Clearly, although novel, this work highlights that further work is needed to adequately address the shortcomings of the available literature.

5. Conclusion

In conclusion, our findings suggest that vitamin C supplementation can significantly improve lipid profile by decreasing TG and TC. However, vitamin C failed to significantly influence LDL and HDL. The benefits on lipid profile manifest from vitamin C supplementation are more likely to benefit from those enrolled in long-term vs. short term interventions. Additional long-term and high-quality RCTs conducted in individuals with different serum concentrations and dietary intakes of vitamin C are needed to further evaluate and confirm the veracity of these findings.

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