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Review

Vitamin C reduces interleukin-6 plasma concentration: a systematic review and meta-analysis of randomized clinical trials

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SUMMARY

Background: Interleukin 6 is an important biomarker for distinguishing high-risk and low-risk patients, and is a constituent of the Nutrition Risk in the Critically Ill (NUTRIC) Score. Studies have indicated the beneficial effects of vitamin C on lowering IL-6 levels and reducing cytokine storm. However, there is still controversy about the exact effect, appropriate route, and dose of vitamin C usage. This meta-analysis was conducted to evaluate the current evidence base relating to vitamin C intervention on decreasing IL-6 levels.

Methods: A systematic search was performed in PubMed, Scopus, Google Scholar, and Cochran databases, from database inception to July 3rd 2021, to obtain any possible randomized clinical trial for inclusion. After screening and removing unrelated and duplicate articles, 24 eligible articles remained for statistical analysis.

Results: We found a significant lowering effect of vitamin C supplementation on IL-6 levels via peroral (PO) (WMD = -0.29 pg/l,

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95% CI [-0.42, -0.16], *P<0.0001*) and intravenous (IV) routes with (WMD = -7.99 pg/l, 95% CI [-8.36, -7.62], *P<0.0001*).
Conclusions: Vitamin C, at doses of 250–1000 mg/day and for less than one week of treatment, regardless of the route of administration, reduces IL-6 levels in participants.

1. Introduction

Inflammatory responses triggered by rapid viral replication and cellular destruction can employ macrophages and monocytes and provoke the release of cytokines and chemokines. Subsequently, cytokines and chemokines activate immune responses, leading to cytokine storms and other metabolic exacerbations [1]. Among cytokines, Interleukin-6 (IL-6) is reported to be significantly associated with a high risk of the development of severe illness conditions [2–4]. Furthermore, IL-6 is an important biomarker in Nutrition Risk in the Critically Ill (NUTRIC) Score [5,6] and stimulates the production of acute-phase proteins in different inflammatory conditions [7]. Serum IL-6 levels in normal healthy people is 5–15 pg/ml [8], however, Yang and colleagues' study on rheumatoid arthritis patients showed that IL-6 levels can raise to 102 pg/ml in this inflammatory condition [9]. In cytokine storm syndrome, the levels of IL-6 can raise to 1000 pg/ml [10], and clinical improvement has been observed following reducing the IL-6 levels with IL-6 receptor antagonist [11]. After IL-6 is produced in the injury area in the initial phase of inflammation, it is conducted to the liver via the blood circulation, followed by the quick induction of a wide range of acute-phase proteins like C-reactive protein (CRP), serum amyloid A [12], fibrinogen, haptoglobin, and α1-antichymotrypsin [13]. Also, this cytokine can elicit chronic inflammation by the employment of monocytes to the zone of inflammation [14].

Vitamin C has anti-oxidant activity, provides support for the immune system [15,16], exerts antiviral characteristics [17,18], enhances neutrophil's phagocytic capacity, chemotaxis, and supports lymphocyte proliferation [1,19,20]. During sepsis, plasma levels of vitamin C are notably depleted or even not measurable [21–23]. Studies have shown that vitamin C can impede the production of IL-6 [23,24], and has potent effects on diminishing inflammatory status [25,26].

However, to our knowledge, no meta-analysis has examined the impacts of the dose, duration, and administration route of vitamin C supplementation on IL-6 levels in patients with severe respiratory illness and other conditions. We conducted this systematic review and meta-analysis to evaluate this effect of vitamin C and determine the appropriate dose, duration, and administration route of vitamin C usage for this purpose.

2. Methods

We completed this study conforming to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines [27]. This study sought to assess the probable mechanism of the advantageous effects of vitamin C through decreasing IL-6 concentrations in patients and to determine the appropriate dose, duration, and administration route of vitamin C usage for this purpose. PubMed, Google Scholar, Scopus, and Cochrane databases were searched from database inception to 3rd July 2021. Using "AND" and "OR" Boolean operators, we searched the following search terms: ("Sodium Ascorbic Acid" OR "L-Ascorbic Acid" OR "Acid, L-Ascorbic" OR "L Ascorbic Acid" OR "Vitamin C" OR "Ascorbate" AND "Interleukin-6" OR "IL6" OR "B-Cell Stimulatory Factor" OR "B-Cell Stimulatory Factor-2" OR "IL-6").

Among the studies, all randomized clinical trials (RCTs) that were conducted in diverse population groups including children, schoolchildren, adults, males, and females; used vitamin C as intervention; had measured IL-6 levels (reported mean and standard deviation or standard error); and had placebo

or control group were included in this study. No date, language, country, or route of administration restriction was applied. Animal studies, cell culture experiments, in vitro supplementation, secondary studies, studies that had used fruit juice instead of vitamin C, co-interventions of vitamin C with another nutrient or active substance, editorials, commentaries, case reports, and studies without the full-text accessibility were not reviewed.

Articles were reviewed based on the title, abstract, and full text, independently, by three authors (MG, SS, and FK), and any instances of disagreement were resolved by consensus with the senior author (KDj). We displayed the selection process in Figure 1.

Habbu's checklist [28] was applied for qualitative assessment of the studies. Nineteen items are included in this checklist. If all criteria were present, the maximum mark of nineteen was achieved. Studies with scores lower than twelve were excluded from the study. Therefore, the minimum and the maximum scores were twelve and nineteen, respectively.

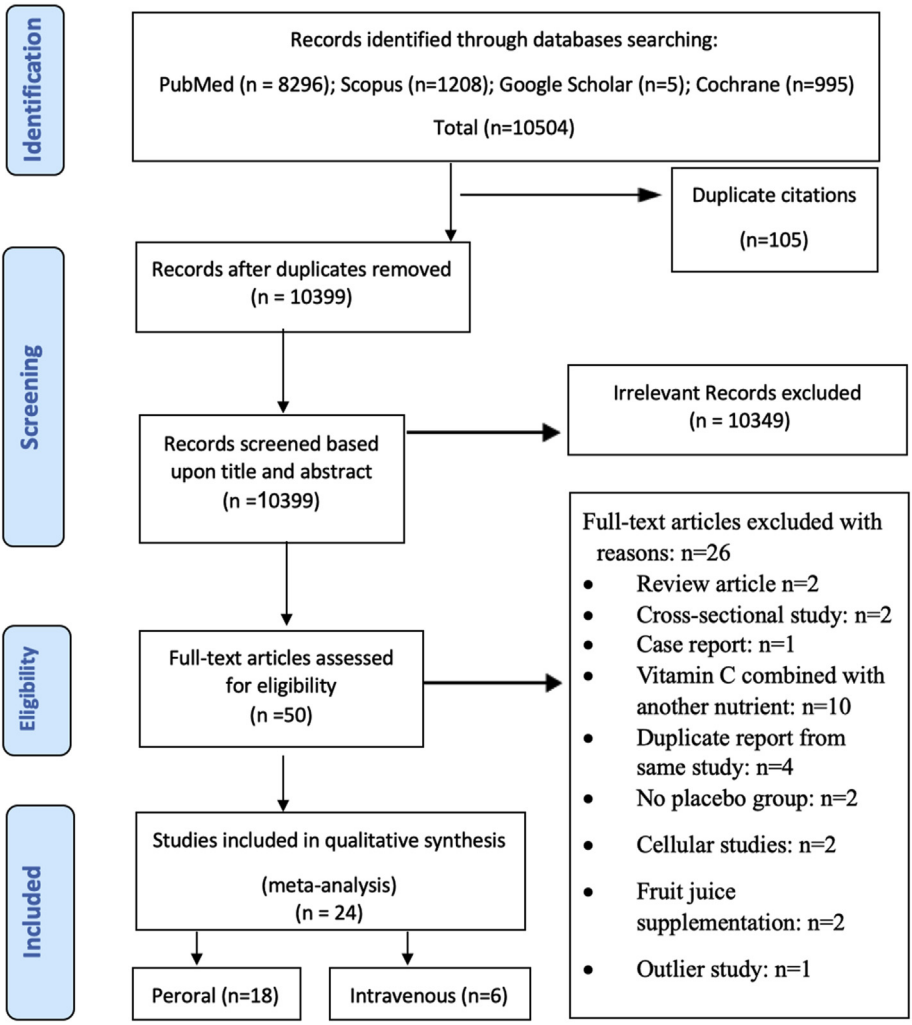

Figure 1. Literature search and filtering of studies according to the PRISMA flow diagrams.

Statistical analyses were carried out using Stata version fourteen (Stata Corporation) software. The effect size was used for quantitative measurement of the magnitude of the mean difference between groups and 95% confidence intervals (CI) were calculated. Statistical heterogeneity was assessed with I^2 between 0 and 100%. We considered $I^2 = 0\%$, without heterogeneity; $I^2 \leq 25\%$, low heterogeneity; $I^2 < 50\%$, moderate heterogeneity; and $I^2 > 75\%$, high heterogeneity [29]. To discern the source of heterogeneity, for groups, we performed subgroup analysis based on dose, duration, and conditions of vitamin C administration. To further assess causes of heterogeneity, a sensitivity analysis was done, in which the consequential deletion of individual studies was performed to examine the power of a single study on the overall effect of vitamin C usage on IL-6 levels. The risk of bias was evaluated using Stata software. Random effects meta-regression was used to explain the influence of age on the effectiveness of vitamin C for lowering IL-6 levels.

3. Results

According to the specified search criteria, 10504 articles were obtained, including 1208 articles from Scopus, 8296 articles from PubMed, 995 articles from Cochrane, and five articles from Google Scholar. After deleting duplicate articles, 10399 articles remained. Subsequently, screening was done on the remaining articles according to the form prepared, considering the Population, Intervention, Comparison, Outcome and Study design (PICOS) framework. Finally, twenty-four eligible articles were included in our systematic review and meta-analysis, eighteen articles for peroral and six articles for intravenous administration (Figure 1).

3.1. Characteristics of included studies

The studies included 801 participants, aged 20–68 years, from four continents; most studies were conducted in Europe and Asia. Baseline sample sizes ranged from 8 - 68 participants. Specifications of included articles are described in Table 1. Six studies are included for IV and eighteen studies are included for PO, respectively. The places of studies were in Iran (n=6), UK(n=6), US (n=3), Spain (n=2), Africa (n=2), Greece (n=1), Mexico (n=1), Palestine (n=1), Egypt (n=1), and Sweden (n=1). The conditions of patients that studies were carried out were in athletes, diabetes mellitus (DM), DM with obesity, DM with cardiovascular disease (CVD), depression, atrial fibrillation (AF), coronary artery bypass surgery (CABG), and ischemic reperfusion injury. The duration of studies was from one day in athletes, before and after exercise, up to 60 days in depressed people.

3.2. Effect of vitamin C supplementation on plasma ascorbic acid levels

Seventeen out of twenty-four included studies had measured plasma ascorbic acid levels before and after vitamin C supplementation. Analysis showed a significant *(P=0.000)* increase of plasma ascorbic acid levels after vitamin C supplementation (WMD = 33.86 μm/L, 95% CI [33.80, 33.93], (Figure 2). in subgroup analysis by dosage, it showed that all supplemented doses of vitamin C (except 1500 mg/d) have increased significantly plasma ascorbic acid levels.

3.3. Effect of vitamin C supplementation on IL-6 levels in oral route

The primary analysis on peroral studies showed a significant effect (*P<0.0001)* of vitamin C on IL-6 levels (WMD = -0.29 pg/l, 95% CI [-0.42, -0.16]. Furthermore, we found low heterogeneity ($I^2 = 19.6\%$), (Figure 3). In the sensitivity analysis for finding the source of heterogeneity, there was no significant heterogeneity between studies (Figure 4). Therefore, subgroups analysis was done based on predefined criteria including the dose of vitamin C, duration of the treatment, and patients' conditions.

In dosage subgroup analysis, significant negative association was observed at low doses 200–250 mg/d, 400–500 mg/d and 1000 mg/d (WMD = -0.91 pg/ml, 95% CI = [-1.44, -0.37], $P < 0.001$; WMD = -0.22 pg/ml, 95% CI = [-0.38, -0.05], *P<0.01* and WMD = -0.58 pg/ml, 95% CI = [-0.92, -0.24], *P<0.001*), respectively (Appendix 1).

Table 1
Characteristic of enrolled studies in the meta-analysis.

Author	Year	Country	Sample size	Mean age	Sex	Dose mg/day	Duration of treatment (day)	[a]Difference in IL-6 levels before and after intervention in intervention group (Pg/ml)	[b]Difference in IL-6 levels before and after intervention in placebo group (Pg/ml)	Conditions	Route
David C. Nieman [50]	1997	US	12	37.7	M/F	1000	8	9.21 & 1.82	**11.2 &7.36**	Athletes	PO
David C. Nieman [51]	2000	South Africa	17	39.7	M/F	500	7	3.69 & 3.7	**3.69 & 3.69**	Athletes	PO
David C. Nieman [51]	2000	South Africa	19	39.7	M/F	1500	7	2.11 & 3.6	**3.7 & 3.69**	Athletes	PO
E. M. Peters [52]	2000	South Africa	16	40.65	M/F	1000	7	12.1 & 30.47	14.22 & 32	Athletes	PO
Thompson, D [53]	2001	UK	16	24	M	400	14	0.7 & 0.63	**0.81 & 0.72**	Athletes	PO
David c. Nieman [54]	2002	US	28	47.55	M/F	1500	7	1.3 & 46.5	**1.3 & 36.1**	Athletes	PO
C. Antoniades [55]	2003	Greece	37	64.2	M/F	2000	60	5.2 & 4.3	**8.1 & 6**	DM & CAD	PO
C. Antoniades [55]	2003	Greece	17	61.36	M/F	2000	60	1.99 & 2.86	2.4 & 3.5	DM & CAD	PO
D. Thompson [56]	2003	UK	16	23.95	M	400	3	2.16 & 13.69	**2.95 & 12.41**	Athletes	PO
C. Antoniades [55]	2003	Greece	21	59	M/F	2000	60	0.81 & 0.8	**0.85 & 0.89**	DM2 & CAD	PO
D. Thompson [30]	2004	UK	14	23.95	M	400	14	0.7 & 0.61	**0.83 & 0.7**	Athletes	PO
Qing LU [57]	2005	Sweden	17	54	M/F	3000	14	3.3 & 3.6	**3.7 & 3.9**	DM	PO
Glen Davison [58]	2006	UK	9	26	M	1000	14	0.6 & 5.5	**0.6 & 5.8**	Athletes	PO
Glen Davison [59]	2007	UK	8	20	M	1500	1	3.3 & 8.6	**3 & 8.5**	Athletes	PO
babk nakhostini roohi [60]	2008	Iran	16	21.75	M	500	1	1.2 & 1.2	**1.35 & 1.48**	Healthy	PO
Abolghassem Jazayery [61]	2011	Iran	31	48	M	200	60	**16.81 & 18.32**	**16.9 & 19.36**	DM	PO
Abolghassem Jazayery [61]	2011	Iran	34	48	M	200	60	**15.55 & 17.06**	**17.94 & 17.37**	DM	PO
Shahab Bohlooli [62]	2012	Iran	16	21.8	M	500	1	**1.18 & 1.17**	**1.33 & 1.47**	Healthy	PO
Farahnaz Khajehnasiri [63]	2012	Iran	68	29.47	M	250	60	**1.32 & 1.47**	**1.487 & 1.6**	Healthy	PO
Farahnaz Khajehnasiri [63]	2012	Iran	68	30.71	M	250	60	**1.233 & 1.23**	**0.928 & 1.78**	Healthy	PO
Absalon D. Gutierrez [64]	2013	Mexico	8	49	M/F	250	14	**1.65 & 1.98**	**1.7 & 2.25**	DM	PO
Absalon D. Gutierrez [64]	2013	Mexico	8	49	M/F	500	14	**1.26 & 2.46**	**1.7 & 2.25**	DM	PO
Absalon D. Gutierrez [64]	2013	Mexico	8	49	M/F	1000	14	**1.34 & 2.8**	**1.7 & 2.25**	DM	PO
Antoni Aguiló [65]	2014	Spain	31	38.35	M	500	14	**1.28 & 1.63**	**1.29 & 1.86**	Athletes	PO
Mohammed S Ellulu [66]	2015	Palestine	64	40	M/F	1000	60	**2.2 & 1.4**	**1.95 & 2.01**	HTN & DM	PO
Ignacio Ferrón-Celma [67]	2010	Spain	20	66.45	M/F	1350	6	**16.4 & 11.9**	9.3 & 15.6	SS	IV
Reza Jouybar [68]	2011	Iran	40	56.9	M/F	6000	3	**502.3 & 57.1**	350.5 & 359.7	CABG	IV
Mahmoud Hassan Mohamed [69]	2015	Egypt	60	35.5	M/F	1000	1	**2.7 & 5.3**	2.9 & 13.3	LLS	IV
Masoumeh Kazemi [70]	2015	Iran	39	37	M/F	13200	1	4.76 & -15.23	-10.34 & 13.13	DDs	IV
Cory R. Trankle [71]	2020	US	20	62.75	M	200	1	**1.65 & 16.43**	1.51 & 8.45	AFA	IV
Damian M. Bailey	**2006**	UK	22	68	M/F	2000	1	**16.4 & 11.9**	9.3 & 15.6	LLS	IV

AP, Acute pancreatitis; SIR, surgical ischemia-reperfusion; CABG, Coronary Artery Bypass Graft Surgery; SS, Septic shock, CAD; coronary artery disease; DM, Diabetes mellitus; LLS, lower limb surgery; DDs, Deceased Donors; HTN, hypertension; AFA, Atrial Fibrillation Ablation; PO, Peroral; IV, intravenous.
[a, b] This colums show plasma concentration of IL-6 in intervention and placebo groups before and after vitamin C and placebo supplementatio, repectively.

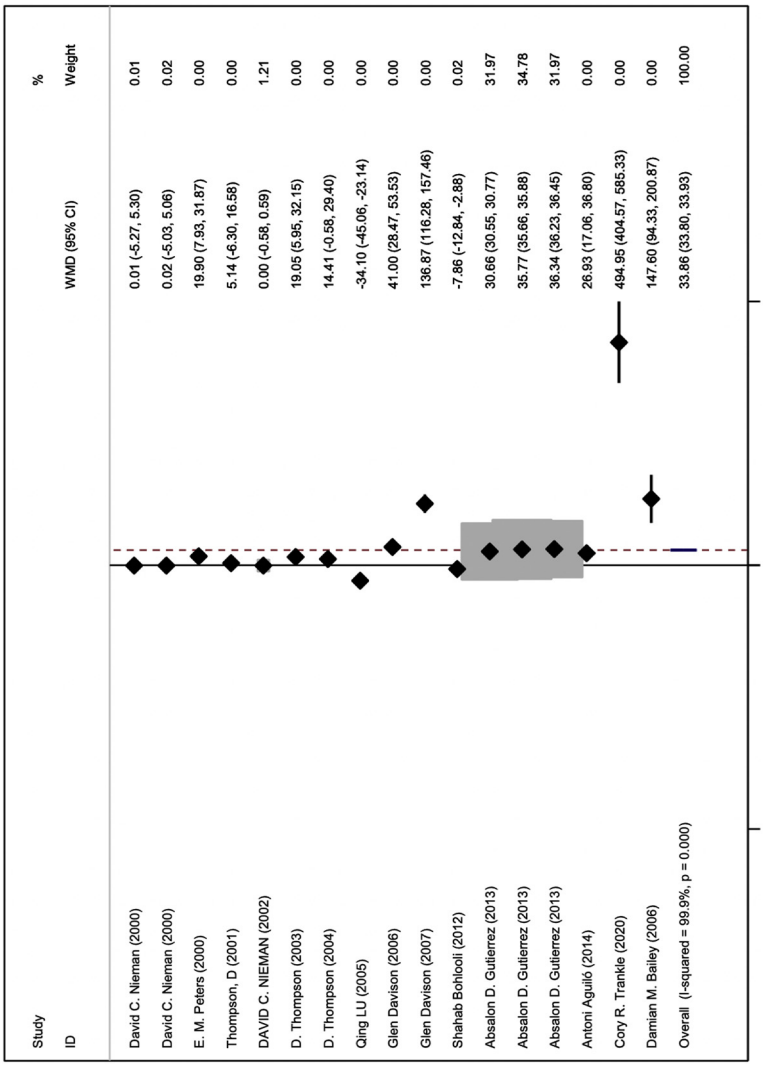

Figure 2. Effect of vitamin C supplementation on plasma ascorbic acid levels.

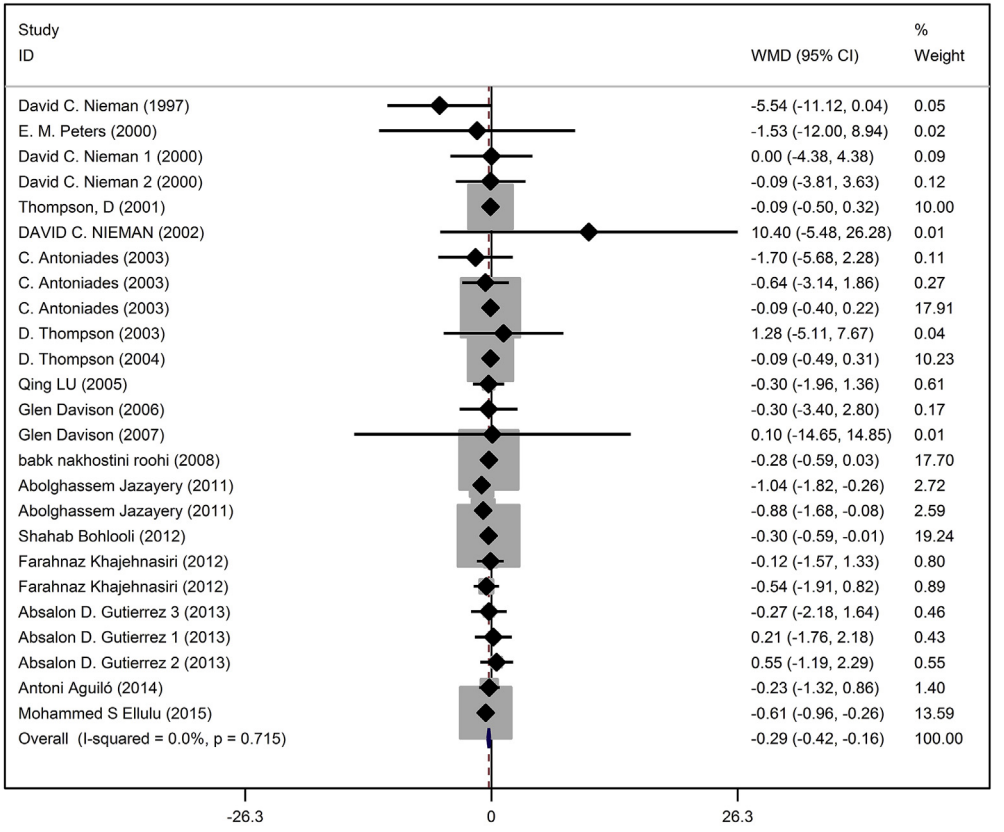

Figure 3. Efficacy of vitamin C supplementation on reducing IL-6 levels in studies that supplemented by peroral.

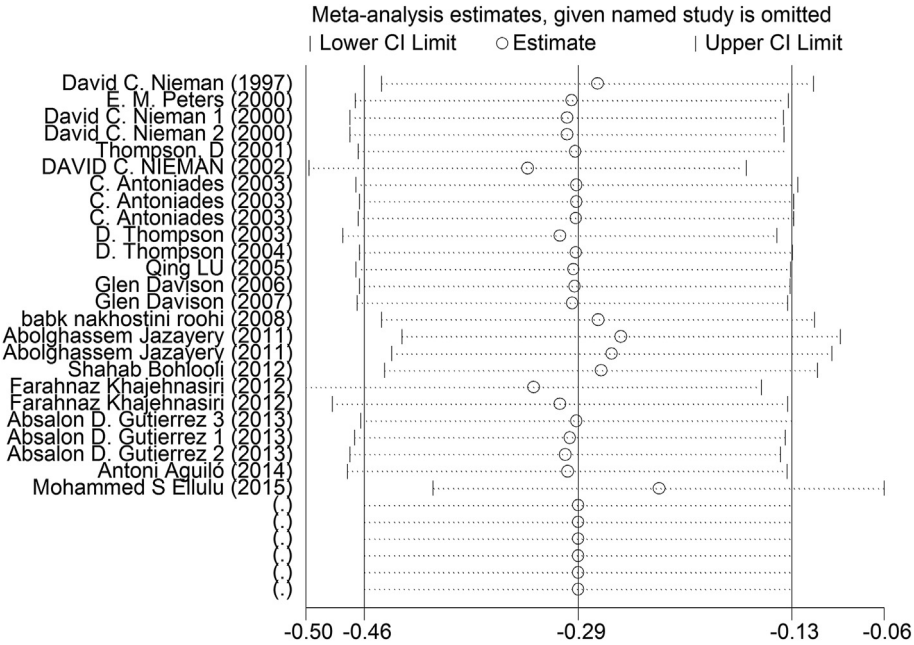

Figure 4. Sensitivity analysis for finding the weight of studies. In subgroup by duration, 7 up to 10 days supplementation pooled together.

In subgroup analysis by duration, a significant negative association was observed in short term (less than one week) and long term (in 8 weeks) vitamin C supplementation (WMD = -0.29 pg/ml, 95% CI = [-0.50, -0.08], *P<0.008*); and WMD = -0.68 pg/ml, 95% CI = [-0.96, -0.39], *P<0.0001*), respectively (Appendix 2).

Also, subgroup analysis by condition of patients showed a significant effect of vitamin C on DM [30], DM + obese, and athletes patients (WMD = -0.88 pg/ml, 95% CI = [-1.40, -0.36], *P<0.001*; WMD = -0.61 pg/ml, 95% CI = [-0.96, -0.26], *P<0.001* and WMD = -0.22 pg/ml, 95% CI = [-0.39, -0.05], *P<0.01*), respectively (Appendix 3).

Moreover, the dose-response analysis showed that the lower doses of vitamin C have the greatest effect on IL-6. The trend of significance decreased by increasing the dosage of vitamin C. Furthermore, at doses higher than the highest dose of vitamin C (1500–2000 mg/d), the increase of vitamin C concentration did not change IL-6 plasma levels (Figure 5). Finally, the regression analysis by age did not illustrate a significant association between age variable and plasma IL-6 concentration (*P= 0.23*) (Appendix 4).

Egger and Begg's analysis did not demonstrate a significant bias to report (95%CI: -0.639, 0.417, *P=0.66*). The funnel plot of studies did not show any significant publication bias (Figure 6).

3.4. Effect of vitamin C supplementation on IL-6 levels in intravenous route

Primary analysis on the included manuscripts that used vitamin C intravenously showed a significant negative association between vitamin C supplementation and plasma IL-6 concentration (WMD = -7.97 pg/l, 95% CI [-8.34, -7.60], *P<0.0001*). Furthermore, we noted moderate heterogeneity (I^2 = 70.3%) (Figure 7).

Subgroup analysis by dosage was performed in two categories; greater than 1500 mg/d (shown with number 2) and lower than 1500 mg/d (shown with number 1). Subgroup analysis by dosages showed significant association between intravenous vitamin C supplementation and IL-6 plasma concentration in lower than 1500 mg/d (WMD = -7.98 pg/l, 95% CI [-8.35, -7.60], *P<0.0001*) (Appendix 5).

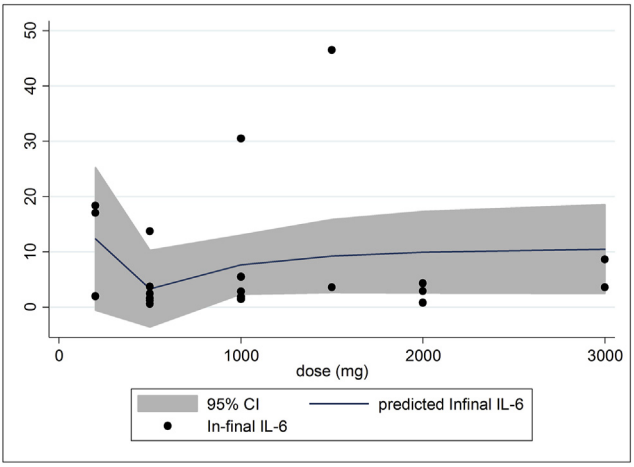

Figure 5. Efficacy of dose-response of vitamin C supplementation on reducing IL-6 levels.

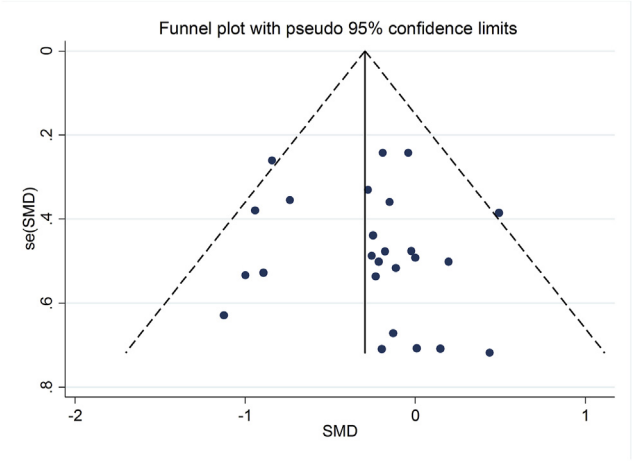

Figure 6. Funnel plot analysis for finding possible bias in the report.

Subgroup analysis by patients' condition demonstrated that vitamin C supplementation significantly decreased IL-6 plasma concentration in sepsis, ischemic reperfusion surgery, and BDD patients (WMD = -302.60 pg/ml, 95% CI = [-510.85, -94.34], *P<0.004)*; (WMD = -7.98 pg/ml, 95% CI = [-8.35, -7.61], *P<0.0001)* and (WMD = -28.37 pg/ml, 95% CI = [-48.09, -8.65], *P<0.005*), respectively (Appendix 6).

The Egger test did not show any significant bias in the report (95% CI: -4.02, 2.65, *P =0.56*).

4. Discussion

This systematic review and meta-analysis evaluated the current evidence base relating to vitamin C intervention on decreasing IL-6 levels in inflammatory diseases, and determined the appropriate dose, duration, and administration route of vitamin C usage for this purpose. We found that vitamin C has a prominent and statistically significant lowering effect on IL-6 levels via the oral route in Diabetic

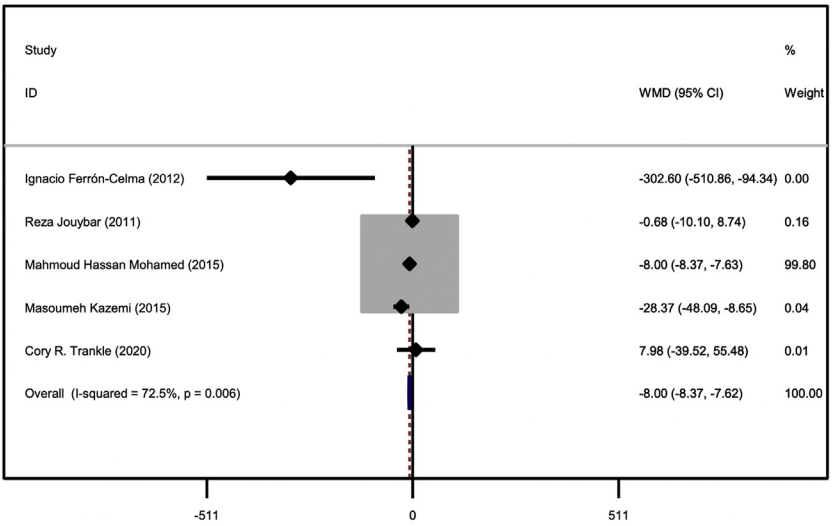

Figure 7. Efficacy of vitamin C on reducing IL-6 levels in studies that supplemented Vitamin C intravenously.

Mellitus patients, athletes, and inflammatory conditions. The most effective dosage was 200–500 and 1000 mg/d via the oral route. Also, in the intravenous route, we found a significant effect in dosages lower than 1500 mg/d in sepsis, ischemic reperfusion surgery, and BDD conditions.

In dosage subgroup analysis, a significant inverse association was observed at low doses. A D. Gutierrez *et al.* performed a study in DM patients, and found that 500 up to 1000 mg/d vitamin C supplementation in short durations has an anti-atherosclerotic effect in diabetic patients [31]. Moreover, I Ferrón-Elma *et al.* found that 450 mg/d vitamin C supplementation significantly can decrease plasma IL-6 concentration in patients with abdominal surgery and sepsis conditions [32]. Furthermore, Hiedra R *et al.* administered vitamin C intravenously at a dose of 1 g every 8 h for 3 days and observed a significant decrease in inflammatory markers in COVID-19 patients [33]. Jouybar *et al.* performed a study on Coronary Artery Bypass Graft Surgery patients with 3-gram vitamin C continuously over 12–18 hours, however they did not see any association between vitamin C and IL-6 levels in higher dosages [37]. Nevertheless, our finding did not confirm the finding of Cheng *et al.* [34] who administered high doses of intravenous vitamin C (10–20 g/day and 1500 mg/kg/day) [34]. Notably, overdoses of vitamin C can have adverse effects, such as kidney stones and diarrhea [35]. Moreover, oxalate nephropathy due to administration of high doses of vitamin C has been reported in 2 patients with COVID-19 [36]. The average daily requirement for vitamin C is 75 mg for females and 90 mg for males, whilst the tolerable upper level of vitamin C is 2 gr orally per day for adults [37]. Due to poor absorption of vitamin C orally, it is assumed that higher doses must be administered intravenously. Intravenous administration is suitable for intensive care patients because near all of them have pre-existing intravenous lines. On the other hand, gastrointestinal problems and difficulty in swallowing are common among ICU patients, which can interfere with drug absorption [38].

Subgroup analysis based on duration demonstrated the highest effect in durations <1 week and 8 weeks' duration, respectively. Contrary to our findings, short durations (less than one week) of vitamin C treatment were carried out by Nakhostin *et al.* and were not effective on lowering IL-6 levels in inflammatory states [39]. Our results showed that, in athletes, DM, and patients that were undergoing surgical procedures, vitamin C had a significant reducing effect on IL-6 levels. This finding shows that the indication of vitamin C for lowering IL-6 levels may be more effective in some medical conditions than others.

The mechanism of decrease of IL-6 levels by vitamin C is attributed to its antioxidant properties and inhibitory function on IL-6 producing monocytes. During lipopolysaccharide (LPS)-induced sepsis,

which is brought about by oxidative damage, production of NF-kB is increased, and this transcription factor plays an important role in the overexpression of pro-inflammatory cytokines during sepsis. Indeed, vitamin C can lead to a decreased production of pro-inflammatory cytokines [23].

Accessible data shows that increased levels of IL-6 are notably coupled with adverse clinical consequences, admission in ICU, ARDS, and death in COVID-19 patients [40]. Regarding the possibility of the development of cytokine storm syndrome in the course of the COVID-19 [41,42], and the beneficial effects of vitamin C on the alleviation of inflammation in cytokine storm syndrome [43–45], the results of this study could be extrapolated to COVID-19 patients. Undoubtedly, among the currently available drugs, vitamin C is a suitable and logical option for use to alleviate ARDS [34,46]. Moreover, IL-6 is a biomarker that reduces appetite [47] and increases cachexia in sepsis conditions [48].

To our knowledge, this is the first meta-analysis on the effects of vitamin C administration on IL-6 levels. Additionally, included studies in our meta-analysis were from nearly all continents of the world and performed predefined subgroup analysis. However, this meta-analysis possesses some limitations. While most of the studies have measured plasma levels of IL-6 by ELISA method, only eight studies have reported the type of anticoagulant (EDTA) used in the test tubes for collecting blood samples. A study by Biancotto *et al.* showed a variation in cytokines levels between serum and plasma samples, and that measurement of some cytokines has been affected by diverse anticoagulants used in preparing plasma samples [49]. Not measuring vitamin C plasma concentration before and after the intervention and not defining the time interval between the last dose of vitamin C and measuring plasma IL-6 levels were limitations that were defined in some included studies. However, this is beyond the control of the present study, but does, nevertheless, highlight the need for adequate time interval definitions in subsequent studies.

Conclusion

We found that vitamin C at doses of 250–1000 mg/day; in treatment durations less than one week; in intravenous and peroral administration; and in sepsis, Diabetic Mellitus, athletes, BDD, and reperfusion surgical patients, reduces IL-6 levels.

Authorship

The conception and design of the study performed by MG, SS, KJ, or acquisition of data, or analysis and interpretation of data carried out by MG, KDJ, SS and AA, drafting the article or revising it critically for important intellectual content MG, FK, CC, and KL. final approval of the version to be submitted KDJ, CC, and MG.

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Conflict of interest

There is no conflict of interest to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nutos.2021.09.003.

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