European Journal of Nutrition
https://doi.org/10.1007/s00394-020-02215-2

REVIEW

Effects of vitamin C on oxidative stress, inflammation, muscle soreness, and strength following acute exercise: meta-analyses of randomized clinical trials

Natiele Camponogara Righi[1] · Felipe Barreto Schuch[1,2] · Angélica Trevisan De Nardi[3] · Caroline Montagner Pippi[1] · Geovana de Almeida Righi[1] · Gustavo Orione Puntel[1] · Antonio Marcos Vargas da Silva[1] · Luis Ulisses Signori[1]

Received: 6 December 2019 / Accepted: 26 February 2020

Abstract

Background Vitamin C (ascorbic acid) seems to attenuate the overproduction of reactive species during and after exercises. Yet, no meta-analysis has summarized the magnitude of this effect. The objective of this study was to systematically review the effects of vitamin C supplementation on oxidative stress, inflammatory markers, damage, soreness, and the musculoskeletal functionality after a single bout of exercise.

Methods Major electronic databases were searched, from inception to September 2019, for placebo-controlled randomized clinical trials (RCTs) that evaluated the effects of vitamin C supplementation on oxidative stress parameters, inflammation markers, muscle damage, muscle soreness, and muscle functionality after a single bout of exercise in healthy volunteers. Random-effects modelling was used to compare mean changes from pre- to postexercise in participants that were supplemented with vitamin C versus placebo. Data were reported as standard mean difference (SMD) and 95% confidence interval (CI).

Results A total of 18 RCTs, accounting for 313 participants (62% males, median age = 24 years) were included. Vitamin C supplementation reduced lipid peroxidation immediately (SMD = − 0.488; 95% CI = − 0.888 to − 0.088), 1 h (SMD = − 0.521; 95% CI = − 0.911 to − 0.131) and between 1 and 2 h (SMD = − 0.449; 95% CI = − 0.772 to − 0.126) following exercise. Exercise induced interleukin-6 (IL-6) response was attenuated 2 h (SMD = − 0.764; 95% CI = − 1.279 to − 0.248) and between 1 and 2 h (SMD = − 0.447; 95% CI = − 0.828 to − 0.065) after exercise. No effects of vitamin C supplementation were found on creatine kinase (CK), C-reactive protein (CRP), cortisol levels, muscle soreness, and muscle strength.

Conclusion Vitamin C supplementation attenuates the oxidative stress (lipid peroxidation) and inflammatory response (IL-6) to a single bout of exercise.

Registration PROSPERO (CRD42018094222).

Keywords Ascorbic acid · Athlete · Exercise · Healthy volunteers · Inflammation · Oxidative stress

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00394-020-02215-2) contains supplementary material, which is available to authorized users.

✉ Luis Ulisses Signori
l.signori@hotmail.com

[1] Department of Physiotherapy and Rehabilitation, Postgraduate Program in Functional Rehabilitation, Federal University of Santa Maria-UFSM, Av. Roraima nº 1000, Cidade Universitária, Bairro Camobi, Santa Maria, RS 97105-900, Brazil

[2] Department of Sports Methods and Techniques, Federal University of Santa Maria, Santa Maria, RS, Brazil

[3] Exercise Pathophysiology Laboratory, Postgraduate Program in Cardiology and Cardiovascular Sciences, Federal University of Rio Grande do Sul, Porto Alegre, RS, Brazil

Published online: 11 March 2020

Introduction

Regular exercise has a multitude of benefits for physical and mental health [1, 2], and most are explained by its ability to promote adaptations in various systems, such as cardiovascular, musculoskeletal, endocrine, and nervous [3–5]. Such adaptations also affect the longevity and enhance the quality of life [6]. However, acutely, a single bout of exercise might lead a pro-inflammatory state and cause muscular soreness [7, 8], as a result of lesions of the macro structures of the musculoskeletal system [9, 10].

Oxidative stress is shown, partially, by these inflammatory events, since the higher metabolic demand during exercise induces an increase in the reactive oxygen and nitrogen species (RONS) production [7, 10]. Since the antioxidant system (exogenous and endogenous) is acutely limited, RONS may exceed their capacity, resulting in oxidation of cellular constituents and cellular damage [7, 10]. For example, immediately following an exercise session, there is a plasma increase of inflammatory markers, such as C-reactive protein (CRP) [8] and intracellular proteins, such as creatine kinase (CK) [11]. This inflammatory state often results in the presence of muscle soreness [12] and decreased functionality [7], impacting the performance [13], and to the abandonment of regular exercise practice by beginners [14]. However, in the medium to long term, the greater production of RONS leads to an increase in the endogenous antioxidant system capacity [15, 16], which results in adaptations and muscle remodeling [17], and impacts on mortality reduction [6].

Vitamin C (Ascorbic Acid) supplementation has been used to increase antioxidant capacity and blunt the excessive production of RONS during and shortly following exercise, especially by athletes in sports competitions, although the results are still controversial [13]. Some studies have shown that vitamin C reduces lipid peroxidation [18, 19] and interleukin-6 (IL-6) [20], an inflammatory marker, following exercise. However, these markers were not affected by vitamin C supplementation in other study [21]. A previous study reviewed the effects of antioxidant supplementation on exercise-induced oxidative stress, showing that the results are inconclusive [22]. Furthermore, systematic reviews [23, 24] evaluated the effects of antioxidant supplementation on delayed onset of muscle soreness (DOMS) and found a small reduction following high-dose supplementation [24]. Nonetheless, such reviews considered studies that carried out supplementation with several antioxidants, either alone or combined. Thus, the effects of isolated vitamin C on oxidative stress, inflammatory markers, damage, soreness, and the strength following exercise are still uncertain. The objective of this study was to systematically review the literature on the effects of vitamin C supplementation on oxidative stress, inflammatory markers, damage, soreness, and the musculoskeletal functionality of healthy volunteers after exercise.

Methods

This systematic review was conducted according to the guidelines suggested by the Preference Report Items for Systematic Review and Meta-analyses: the PRISMA statement [25] and followed the recommendations of the Cochrane Handbook [26]. The study was registered in PROSPERO under the number CRD42018094222.

Literature search strategy

The search strategy considered the studies published from inception to September 2019 on MEDLINE (PubMed), EMBASE, Cochrane CENTRAL, Web of Science and Sport Discus databases, without restriction of year of publication or language. The following descriptors were used: “Adult”, “Healthy Volunteers”, “Athletes”, “Ascorbic Acid” and “Exercise”, associated with a highly sensitive search strategy for clinical trials [27]. Also, there was a manual search in included articles’ and previous reviews’ reference lists [23, 24] and on the ClinicalTrials (website). The full search strategy for each database can be found in the Online Supplemental Table 1.

Eligibility criteria

Two reviewers (NCR and ATD) independently assessed the identified studies and selected them, by title and abstract, according to the following inclusion criteria: (1) Placebo-controlled randomized clinical trials (RCTs); (2) evaluated the effects of vitamin C supplementation on oxidative stress parameters, inflammatory markers, muscle damage, muscle soreness and/or muscle functionality (e.g., functional capacity, strength, flexibility, power, endurance, range of motion [ROM], among others) immediately post and over different periods within the next 5 days following an single bout of exercise; (3) included healthy adults (over 18 years), who could be athletes (individuals that exercise regularly to improve performance; that are registered in some sports federation and participate in official sports competitions), active individuals (current exercisers who do not meet the criteria for athlete definition) [28] or untrained, and (4) presented at least one comparison between an intervention group with isolated vitamin C supplementation against a placebo condition, that had been submitted to the same exercise protocol.

The abstracts that potentially met the criteria or that did not provide sufficient information were selected for

full-text evaluation. At this stage, the exclusion criteria were: (1) supplementation interrupted 24 h (h) prior to exercise, due to the fact that 24 h after supplementation, plasma vitamin C concentration returns to basal levels [29]; (2) supplementation performed only following exercise. Disagreements were resolved by consensus and, if necessary, by a third reviewer (LUS).

Data extraction

Through the use of standardized forms, two independent reviewers (NCR and CMP) extracted information on study identification (authors, year of publication, country, funding); sample characteristics (sample size, % of males, age, body mass index); study protocol and interventions data (study design, exercise type, intensity and time) and vitamin C intake (dosage, length of use); outcomes data (oxidative stress parameters, lipoperoxidation, malondialdehyde (MDA), and thiobarbituric acid reactive substances (TBARS), inflammation (IL-6 and CRP), muscle damage (CK), muscular soreness, muscle strength (measured trough maximum voluntary contraction (MVC) and peak torque isometric and isokinetic) and biomarkers from blood tissue, analyzed both on serum and plasma levels (collected from 24 h, 48 h and 72 h following the exercise bout). Outcome data presented in graphs in the original papers were retrieved through PlotDigitizer software for Windows. Divergences between the evaluators were resolved by consensus, or, whenever necessary, by decision of a third reviewer (LUS) was consulted. When necessary, the main authors of the selected studies were contacted for additional information and data.

When considering the studies with more than one intervention groups, the ones with the highest dose of administered vitamin C were extracted, besides the group that underwent supplementation in only 1 day. Studies with standard error values of 0 were adopted for analysis as 0.001.

Risk of bias assessment and quality of evidence

The risk of bias was assessed by two independent reviewers (NCR and CMP), using the tool presented in the Cochrane Handbook for Systematic Reviews of Interventions, version 5.1.0 [26]. The evaluated domains were random sequence generation, concealed allocation, blinding of participants, professionals and evaluators to outcomes, description of losses or exclusions, and selective reporting. For each of the domains, the risk of bias was characterized as "low", "high" or "uncertain". The certainty in the evidence and strength of the recommendations for each outcome was evaluated according to the grading of recommendation, assessment, development and evaluation (GRADE), considering study design, risk of bias, inconsistency of the results, indirectness of evidence, imprecision, and publication bias [30, 31].

Data analysis

The analyses were performed through the Comprehensive Meta-Analysis Software, version 3. A random-effects meta-analysis using the DerSimonian and Laird method was performed, and the data were presented by standard mean difference (SMD) together with 95% confidence intervals (95% CI) as effect size measurement. The SMD was calculated by the difference of the mean values and standard deviation between baseline and postexercise, of the vitamin C versus Placebo groups, for each study, respectively. The analyses were performed for each outcome collected between 0 and 24 h, 24 h, 48 h, and 72 h following exercise, separately. The considered effect sizes were small if SMD > 0.2, moderate if SMD > 0.5 and large if SMD > 0.8, [32] and a p value ≤ 0.05 was considered statistically significant.

Heterogeneity was assessed by the Chi squared test and I squared test (I^2), considered low, moderate, and high when I^2 values were < 25%, 25–50%, and > 50%, respectively [33]. In order to explore the heterogeneity, we performed: (1) sensitivity analyses withdrawing studies with athletes and anaerobic exercise; (2) subgroups analyses, exploring the vitamin C dose (up to 500 mg and > 500 mg), measurement method (for MDA and TBARS), study design (cross and parallel), exercise intensity (moderate and high); and (3) meta-regressions testing the association between gender (%men), age (years) and time of supplementation (in days) with their effects on lipid peroxidation. The publication bias was assessed by Funil visual analysis and the Egger test [34] and adjusted using the Trim and Fill technique [35].

Results

Description of studies

Initially, of the 1165 potentially relevant studies found, 18 RCTs [18–21, 36–49] met the inclusion criteria. The included studies were published between 1993 and 2019 and included a total of 313 participants, with a median age of 24 years (72% men), 13% athletes, 33% active and 54% healthy adults. Figure 1 shows the flowchart, detailing the number of studies excluded for each reason and the main characteristics of the studies are detailed in Table 1.

The supplementation was performed orally in all studies, with dose ranging from 400 to 3000 mg. The period of intake before exercise raged from 1 to 28 days. Aerobic exercise was used in most (83%, $k = 15$) [19–21, 36–38,

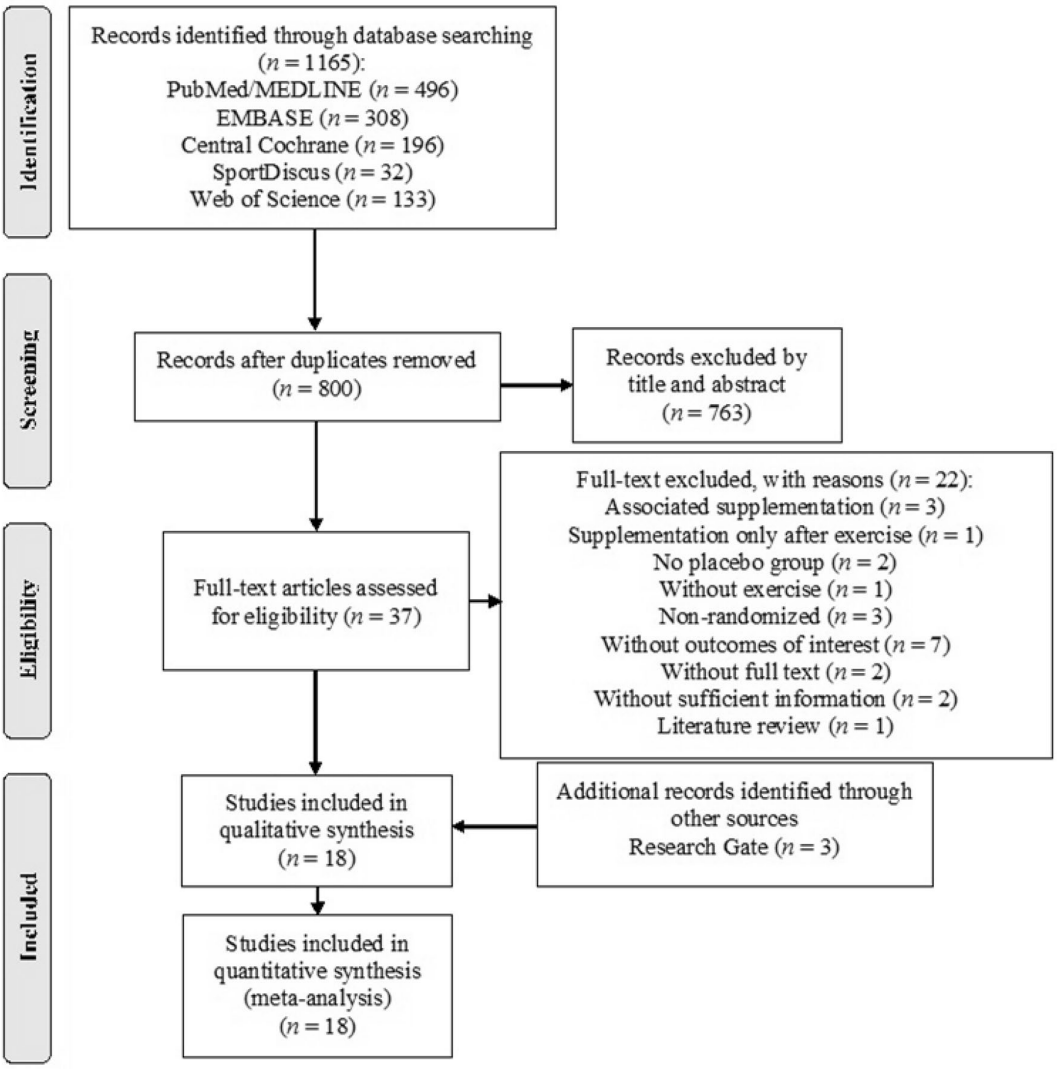

Fig. 1 Flowchart of the study design. *n* sample size

40–45, 47–49] of the studies. Oxidative stress was assessed in 78% ($k = 14$) of the included studies, through lipid peroxidation [18–21, 36, 40–43, 45, 47–49], protein carbonyls [47], enzymes including superoxide dismutase [49], catalase [49], glutathione peroxidase [49], total glutathione [40], and ratio of oxidized to total glutathione [39, 47]. Only lipid peroxidation was meta-analyzed, since it was the only variable evaluated in a sufficient number of RCTs and caused enough controversies in the results section that would justify such meta-analysis. There was the evaluation of IL-6 in 33% ($k = 6$) [19–21, 44, 45, 48] of the studies, CRP in 17% ($k = 3$) [20, 21, 49], CK in 50% ($k = 9$) [18, 20, 21, 38, 39, 43, 44, 48, 49] and cortisol levels in 22% ($k = 4$) [19, 20, 43, 45]. Muscle soreness was evaluated in 39% ($k = 7$) [20, 36, 37, 39, 43, 44, 46] of the studies, through visual scales with different metrics [20, 36, 37, 39, 43, 44, 46] and pressure algometry [36]. Musculoskeletal functionality was assessed in 33% ($k = 6$) [20, 36, 38, 39, 43, 46] of them, through muscle strength [20, 36, 38, 39, 43, 46], ROM [39], flexibility, and muscle tenderness [46]. Functionality was analyzed only by muscle strength, as it was the only variable evaluated in a sufficient number of RCTs to perform the meta-analysis. All selected studies were controlled by placebo and eight of them presented crossover design [19, 37, 41–43, 45, 47, 49]. Eight studies reported information on funding, of which six [21, 37, 40–42, 49] refer to funding for research in universities or public bodies and two [20, 43] were financed by companies. Two studies [36, 38] reported only academic or technical support. In eight included studies [18, 19, 39, 44–48], information on research funding was not reported.

Table 1 Characteristics of included studies

Study, year	Study design	Sample characteristics		Intervention characteristics (vitamin C supplementation)	Type of exercise	Evaluated outcomes
Jakeman and Maxwell, 1993 [38]	Parallel	Vitamin C: ($n=8$), 19.6 (17.9–21.8) years, active men	Placebo: ($n=8$), 19.6 (17.9–21.8) years, active men	400 mg, 28 days	Aerobic: Box stepping (24 steps/min)	Muscle damage (CK), muscle strength (maximal voluntary contraction)
Alessio, Goldfarb and Cao, 1997 [42]	Crossover	Vitamin C: ($n=9$), 33 ± 2.6 years, healthy men	Placebo: ($n=9$), 33 ± 2.6 years, healthy men	1000 mg, 1 day/1000 mg, 14 days	Aerobic: Running on a motorized treadmill at 80% VO_{2max}	Lipid peroxidation (TBARS)
Vasankari et al., 1998 [41]	Crossover	Vitamin C: ($n=9$), 28.6 (20–37) years, athlete men	Placebo: ($n=9$), 28.6 (20–37) years, athlete men	2000 mg, 1 day	Aerobic: 19 km running exercise (4.5 km warming up; 10.5 km maximal, noncompetitive running and 4 km cooling down)	Lipid peroxidation (diene conjugation)
Thompson et al., 2001a [20]	Parallel	Vitamin C: ($n=8$), 25 ± 2 years, active men	Placebo: ($n=8$), 23 ± 2 years, active men	400 mg, 12 days	Aerobic: Loughborough Intermittent Shuttle Test[a] for 90 min	Lipid peroxidation (MDA), inflammation (IL-6, CRP), muscle damage (CK), cortisol, muscle soreness, muscle strength (torque)
Thompson et al., 2001b [43]	Crossover	Vitamin C: ($n=9$), 28.4 ± 1.3 years, active men	Placebo: ($n=9$), 28.4 ± 1.3 years, active men	1000 mg, 1 day	Aerobic: Loughborough Intermittent Shuttle Test[a] for 90 min	Lipid peroxidation (MDA), muscle damage (CK), cortisol, muscle soreness, muscle strength (peak torque)
Thompson et al., 2004 [44]	Parallel	Vitamin C: ($n=7$), 25.3 ± 1.4 years, active men	Placebo: ($n=7$), 22.6 ± 1.7 years, active men	400 mg, 16 days	Aerobic: Running treadmill at 60% VO_{2max} (0% downhill for 15 min + downhill 18% for 30 min)	Inflammation (IL-6), muscle damage (CK), muscle soreness
Goldfarb et al., 2005 [47]	Crossover	Vitamin C: ($n=12$), 25 ± 1.4 years, healthy men	Placebo: ($n=12$), 25 ± 1.4 years, healthy men	500 mg/1000 mg, 14 days	Aerobic: Running for 30 min at 75/80% VO_{2max}	Lipid peroxidation (TBARS)
Bryer and Goldfarb, 2006 [39]	Parallel	Vitamin C: ($n=10$), 21.4 ± 0.8 years, healthy men	Placebo: ($n=8$), 24.4 ± 1.7 years, healthy men	3000 mg, 18 days	Anaerobic: Seventy eccentric actions using the elbow flexors	Muscle damage (CK), muscle soreness, muscle strength (maximal isometric strength)
Close et al., 2006 [36]	Parallel	Vitamin C: ($n=10$), 24 ± 1.5 years, active men	Placebo: ($n=10$), 22.1 ± 0.4 years, active men	1000 mg, 15 days	Aerobic: Downhill running for 30 min at 60% VO_{2max}	Lipid peroxidation (MDA), muscle soreness, muscle strength (peak torque)
Connolly et al., 2006 [46]	Parallel	Vitamin C: ($n=12$), 22.3 ± 3.9 years, healthy men and women	Placebo: ($n=12$), 22.6 ± 4.6 years, healthy men and women	3000 mg, 8 days	Anaerobic: 40 (2×20) maximal eccentric contractions of the elbow flexors	Muscle soreness, muscle strength (maximal isometric strength)

Table 1 (continued)

Study, year	Study design	Sample characteristics		Intervention characteristics (vitamin C supplementation)	Type of exercise	Evaluated outcomes
Davison and Gleeson, 2006 [45]	Crossover	Vitamin C: ($n=9$), 26 ± 2 years, active men	Placebo: ($n=9$), 26 ± 2 years, active men	1000 mg, 14 days	Aerobic: Ride a bicycle for 2.5 h at 60% VO_{2max}	Lipid peroxidation (MDA), inflammation (IL-6), Cortisol
Davison and Gleeson, 2007 [19]	Crossover	Vitamin C: ($n=8$), 20 ± 2.8 years, healthy men	Placebo: ($n=8$), 20 ± 2.8 years, healthy men	1500 mg, 2 days	Aerobic: Ride a bicycle for 2.5 h at 60% VO_{2max}	Lipid peroxidation (TBARS), inflammation (IL-6), Cortisol
Karandish, Rahiden and Moghaddam, 2008 [40]	Parallel	Vitamin C: ($n=25$), 24 ± 3 years, healthy women	Placebo: ($n=24$), 23 ± 2 years, healthy women	500 mg, 14 days	Aerobic: Running for 30 min to 5–6 km h^{-1}	Lipid peroxidation (MDA)
Mizuma et al., 2009 [37]	Crossover	Vitamin C: ($n=14$), 36.7 ± 9.4 years, healthy men and women	Placebo: ($n=14$), 36.7 ± 9.4 years, healthy men and women	3000 mg, 8 days	Aerobic: Bicycle ergometer for 120 min at fixed workloads to reach 80% of target heart rate	Muscle soreness
Bohlooli et al., 2012 [21]	Parallel	Vitamin C: ($n=8$), 21.5 ± 2.2 years, healthy men	Placebo: ($n=8$), 22.1 ± 2 years, healthy men	500 mg, 1 day	Aerobic: Running on treadmill for 30 min at 75% VO_{2max}	Lipid peroxidation (MDA), inflammation (IL-6 e CRP), muscle damage (CK)
Aguiló et al., 2014 [48]	Parallel	Vitamin C: ($n=16$), 37.2 ± 5.4 years, athlete men	Placebo: ($n=15$), 39.5 ± 5.6 years, athlete men	500 mg, 15 days	Aerobic: 15 km run competition	Lipid peroxidation (MDA), inflammation (IL-6), muscle damage (CK)
Poulab et al., 2015 [18]	Parallel	Vitamin C: ($n=10$), 24.15 ± 1.75 years, active men	Placebo: ($n=10$), 24.15 ± 1.75 years, active men	1000 mg, 28 days	Anaerobic: Running on treadmill for 45 min (nine sets of 5 min/2 min rest periods between sets) at 10° downhill and 80% VO_{2max}	Lipid peroxidation (MDA), muscle damage (CK),
Yimcharoen et al., 2019 [49]	Crossover	Vitamin C: ($n=19$), 22.4 ± 2.2 years, healthy women	Placebo: ($n=19$), 22.4 ± 2.2 years, healthy women	1000 mg, 1 day	Aerobic: Cycling to 65–75% of maximum heart rate	Lipid peroxidation (TBARS), inflammation (CRP), muscle damage (CK)

n sample size, *min* minutes, *h* hours, *MDA* malondialdehyde, *CK* creatine kinase, *IL-6* interleukin-6, *TBARS* plasma thiobarbituric acid reactive substances, *CRP* C-reactive protein, VO_{2max} maximal oxygen uptake

[a]Walking, slow running and running

In the period between 0 and 24 h, a study [20] assessed outcomes 1 h and 2 h after exercises, with only the 2-h period being included in the 1 h and 2 h analysis, and another study [49] assessed outcomes 30 min after exercise, being included in the analysis of 1 h.

Quantitative synthesis/meta-analyses

Lipid peroxidation

Lipid peroxidation was evaluated in 13 studies using MDA [18, 20, 21, 36, 40, 43, 45, 48] or TBARS [19, 41, 42, 47, 49] (n = vitamin C: 140/Placebo: 140). Immediately after the exercises, there was a small reduction (SMD = − 0.488; 95% CI = − 0.888 to − 0.088; p = 0.017; n = vitamin C: 140/Placebo: 140; studies = 12; I^2 = 60.60; very low quality of evidence), moderate reduction 1 h (SMD = − 0.521; 95% CI = − 0.911 to − 0.131; p = 0.009; n = vitamin C: 53/Placebo: 53; studies = 5; I^2 = 0; moderate quality of evidence) and small reduction 1 h and 2 h (SMD = − 0.449; 95% CI = − 0.772 to − 0.126; p = 0.006; n = vitamin C: 76/Placebo: 77; studies = 7; I^2 = 0; moderate quality of evidence) after exercises (Fig. 2). Two hours, 24 h, 48 h, and 72 h after exercise, there were no differences between groups (Supplemental Table 2) and based on the GRADE approach, the quality of the evidence for this outcome was considered moderate (to 2 h) and very low to the other moments (Supplemental Table 3). Potential publication bias was found by funnel chart (Supplemental Fig. 1) and Egger's test in lipid peroxidation analyses 0 h (p = 0.022; Trim and Fill adjusted effect size: unchanged) and 24 h (p = 0.038; Trim and Fill adjusted effect size: unchanged). A sensitivity analysis removing two studies with athletes [41, 48] and one study that performed anaerobic exercise [18] did not change the results in the lipid peroxidation immediately following exercise.

The subgroups were analyzed regarding the supplementation dose, with a group of studies that used doses up to 500 mg [20, 21, 40, 48] (SMD = − 0.265; 95% CI = − 0.956 to 0.425; p = 0.451; n = vitamin C: 57/Placebo: 55; studies = 4; I^2 = 0) and greater than 500 mg [18, 19, 41–43, 45, 47, 49] (SMD = − 0.624; 95% CI = − 1.43 to − 0.105; p = 0.018; n = vitamin C: 83/Placebo: 85; studies = 8; I^2 = 0), with no evidence of differences between them, but with reduction of lipid peroxidation only in the subgroup of doses greater than 500 mg. The same happened with the subgroups related to method of measurement of lipid peroxidation, MDA [18, 20, 21, 40, 43, 45, 48] (SMD = − 0.348; 95% CI = − 0.867 to 0.196; p = 0.205; n = vitamin C: 85/Placebo: 83; studies = 7; I^2 = 33.94) and TBARS [19, 41, 42, 47, 49] (SMD = − 0.713; 95% CI = − 0.368 to − 0.057; p = 0.033; n = vitamin C: 55/Placebo: 57; studies = 5; I^2 = 77.74) and subgroups of exercise intensity, moderate [19, 21, 45] (SMD = − 0.340; 95% CI = − 1.024 to 0.343; p = 0.329; n = vitamin C: 25/Placebo: 25; studies = 3; I^2 = 31.15) and high [18, 20, 42, 43, 47] (SMD = − 1.039; 95% CI = − 2.023 to − 0.054; p = 0.039; n = vitamin C: 46/Placebo: 44; studies = 5; I^2 = 78.86), with no evidence of differences between them, but with reduction of lipid peroxidation only in the subgroup of TBARS and high intensity. Meta-regressions did not correlate gender, age, and time of supplementation with the effects of vitamin C supplementation on lipid peroxidation immediately after exercise.

Inflammatory markers

The evaluation of IL-6 and CRP included six [19–21, 44, 45, 48] (n = vitamin C: 55/Placebo: 56) and three [20, 21, 49] (n = vitamin C: 35/Placebo: 35) studies, respectively. The IL-6 2 h following exercise presented a moderate reduction (SMD = − 0.764; 95% CI = − 1.279 to − 0.248; p = 0.004; n = vitamin C: 31/Placebo: 32; studies = 3; I^2 = 0; moderate quality of evidence) and a small reduction in the interval between 1 and 2 h after exercise (SMD = − 0.447; 95% CI = − 0.828 to − 0.065; p = 0.022; n = vitamin C: 55/Placebo: 56; studies = 6; I^2 = 0.08; moderate quality of evidence) (Fig. 2) when compared with controls. Immediately, 1 h, 24 h, and 48 h following exercise there was no difference between the groups supplemented with vitamin C and placebo (Supplemental Table 2) and based on the GRADE approach, the quality of the evidence for this outcome was considered moderate in these moments. The CRP showed no difference between the groups at the evaluated moments, with moderate quality of the evidence (Supplemental Table 3).

Muscle damage

Nine studies [18, 20, 21, 38, 39, 43, 44, 48, 49] (n = vitamin C: 93/Placebo: 92) assessed muscle damage from CK levels. Immediately, 1 h, 2 h, 24 h, 48 h, and 72 h after exercise, there was no difference between groups supplemented with vitamin C and placebo (Supplemental Table 2) and based on the GRADE approach, the quality of the evidence for this outcome was considered very low (to 24 h) and moderate compared to the other moments (Supplemental Table 3). Potential publication bias was found by funnel plot examination (Supplemental Fig. 1) and by the Egger test in CK analysis 24 h after exercise (p = 0.011; Trim and Fill adjusted effect size: − 0.525; 95% CI = − 0.945 to − 0.105; Studies Trimmed: 2).

Cortisol

Four studies [19, 20, 43, 45] evaluated cortisol levels (n = vitamin C: 33/Placebo: 33) immediately, 1 h, 1 h, and

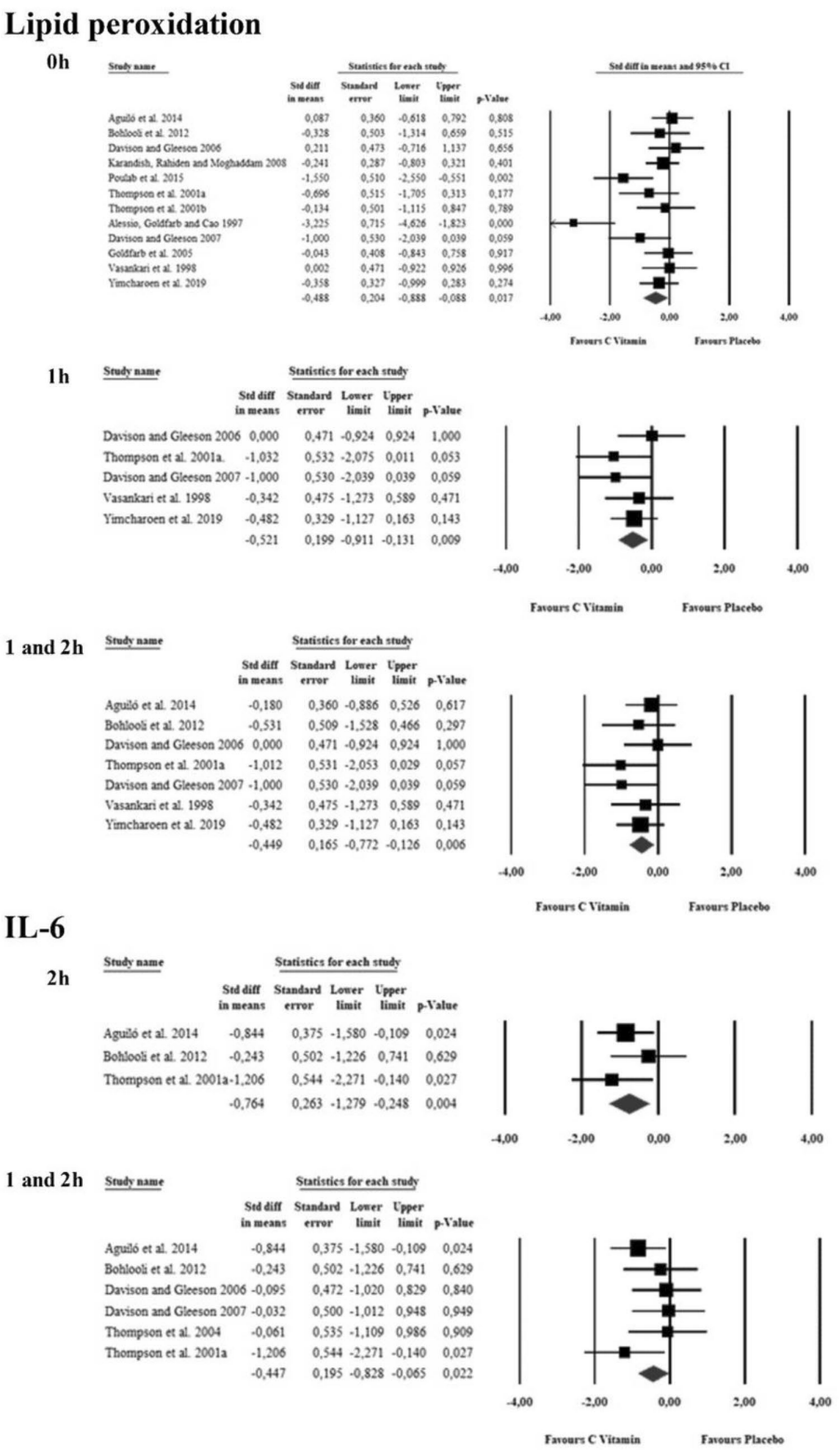

Fig. 2 Effect of vitamin C supplementation on lipid peroxidation and IL-6. *Std diff in means* standard mean difference; *95% CI* 95% confidence intervals

2 h, 24 h, 48 h and 72 h after exercise. In none of the evaluated moments, differences between the supplements (Supplemental Table 2) were observed and based on the GRADE approach, the quality of the evidence for this outcome was considered very low (to immediately, 1 h and 2 h, 24 h), low (to 1 h) and moderate (to 48 h and 72 h) (Supplemental Table 3). Potential publication bias was found by funnel plot (Supplemental Fig. 1) and by Egger test on cortisol analysis immediately following exercise ($p = 0.013$; Trim and Fill adjusted effect size: -0.045; 95% CI = -0.722 to 0.632; Studies Trimmed: 1).

Muscle soreness

Seven studies [20, 36, 37, 39, 43, 44, 46] (n = vitamin C: 70/Placebo: 68) evaluated muscle soreness. The meta-analysis results showed no difference between the groups supplemented with vitamin C and placebo immediately, 4 h, 24 h, 48 h, and 72 h after exercise (Supplemental Table 2) and based on the GRADE approach, the quality of the evidence for this outcome was considered very low (to 24 h), low (to immediately and 48 h) and moderate (to 4 h and 72 h) (Supplemental Table 3).

Muscle strength

Muscle strength was assessed through the MVC [38, 39, 46] (n = vitamin C: 30/Placebo: 28) and isometric [43] and isokinetic [36] peak torque (n = vitamin C: 19/Placebo: 19). Immediately, 24 h, 48 h and 72 h after exercise, no difference was observed between groups supplemented with vitamin C and placebo (Supplemental Table 2). Based on the GRADE approach, the quality of the evidence for this outcome was considered very low (to MVC—24 h), low (to 72 h) and moderate to the other moments (Supplemental Table 3). Potential publication bias was found by visual examination of the funnel plot (Supplemental Fig. 1) and the Egger test in the analysis of MVC 72 h ($p = 0.010$; Trim and Fill adjusted effect size: unchanged).

Assessment of risk of bias and quality of evidence

The assessment of risk of bias in the included studies is shown in Table 2. Information on the randomization method and concealed allocation was unclear in the studies. Seventy-two percent reported blinding of participants and of involved staff and 61% of outcome assessors. Most studies (83.3%) were classified with low risk of bias for the

Table 2 Risk of bias of included studies

Study, year	Bias domains					
	Randomization	Allocation concealment	Blinding (participants and personnel)	Blinding (outcome assessment)	Incomplete outcome data	Selective reporting
Jakeman and Maxwell, 1993 [38]	Unclear	Unclear	Low	Low	Low	Unclear
Alessio, Goldfarb and Cao, 1997 [42]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Vasankari et al., 1998 [41]	Unclear	Unclear	Low	Unclear	Low	Unclear
Thompson et al., 2001a [20]	Unclear	Unclear	Low	Low	Low	Unclear
Thompson et al., 2001b [43]	Unclear	Unclear	Low	Low	Low	Unclear
Thompson et al., 2004 [44]	Unclear	Unclear	Low	Low	Low	Unclear
Goldfarb et al., 2005 [47]	Unclear	Unclear	Low	Low	Low	Unclear
Bryer and Goldfarb, 2006 [39]	Unclear	Unclear	Unclear	Unclear	Low	Unclear
Close et al., 2006 [36]	Unclear	Unclear	Low	Low	Low	Unclear
Connolly et al., 2006 [46]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Davison and Glesson, 2006 [45]	Unclear	Unclear	Low	Unclear	Low	Unclear
Davison and Glesson, 2007 [19]	Unclear	Unclear	Low	Unclear	Unclear	Unclear
Karandish, Rahiden and Moghaddam, 2008 [40]	Unclear	Unclear	Unclear	Low	Low	Unclear
Mizuma et al., 2009 [37]	Unclear	Unclear	Low	Low	Low	Unclear
Bohlooli et al., 2012 [21]	Unclear	Unclear	Low	Low	Low	Unclear
Aguiló et al., 2014 [48]	Unclear	Unclear	Low	Low	Low	Unclear
Poulab et al., 2015 [18]	Unclear	Unclear	Low	Low	Low	Unclear
Yimcharoen et al., 2019 [49]	Unclear	Unclear	Unclear	Unclear	Low	Low

Low low risk of bias, *High* high risk of bias, *Unclear* no information or uncertainty over the potential for bias

Table 3 A summary of GRADE's approach to rating quality of evidence

Analysis	Quality assessment						Quality	Importance
	Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision		
Lipid peroxidation								
0 h	12	RCT	Not serious	Very serious[b]	Not serious	Serious[a]	Very low	Important
1 h	5	RCT	Not serious	Not serious	Not serious	Serious[a]	Moderate	Important
1–2 h	6	RCT	Not serious	Not serious	Not serious	Serious[a]	Moderate	Important
IL-6								
2 h	3	RCT	Not serious	Not serious	Not serious	Serious[a]	Moderate	Important
1–2 h	6	RCT	Not serious	Not serious	Not serious	Serious[a]	Moderate	Important

h hours, *IL-6* interleukin-6, *RCT* randomized clinical trial

[a]Few studies and small sample

[b]High heterogeneity (over 50%)

domain: incomplete outcome data. In summary, the risk of bias for each study was considered unclear.

The quality of the evidence for each estimate of the effect of the result was evaluated through the GRADE system, indicating moderate quality in most analyses. The quality assessment is shown in Table 3.

Discussion

To our knowledge, this is the first systematic review to exclusively analyze the role of vitamin C on lipid peroxidation, inflammatory markers, muscle soreness, and the muscle functionality of healthy volunteers following a single bout of exercise. This study shows that vitamin C supplementation decreases lipid peroxidation and the inflammatory response (IL-6) immediately (lipid peroxidation) and in the interval between 1 and 2 h (lipid peroxidation and IL-6) following exercise when compared to placebo, although it shows no effects on muscle damage, cortisol levels, CRP, or muscle soreness and strength.

Vitamin C supplementation blunted lipid peroxidation immediately and in the interval between 1 and 2 h following exercise. This can be explained by the neutralizing effect of vitamin C on RONS, due to its direct effects, eliminating superoxide, and its indirect effects, attenuating hydrogen peroxide [50]. Also, vitamin C seems to restore α-tocopherol (vitamin E), which is another inhibitor of lipid peroxidation [51]. Supplementation with antioxidants is performed with the objective of assisting the endogenous antioxidant system in protecting the body against oxidative stress that occurs during and after high intensity physical exercises. In addition, some controversies regarding the vitamin C supplementation are caused by the diversity of dosage and supplements [23]. We explored the role of different dosages and have found that supplementation with higher doses (> 500 mg) of vitamin C seems to be more effective in reducing oxidative stress immediately after exercise, since it reduces lipid peroxidation. These results are corroborated by previous RCTs [18, 49], Goldfarb and colleagues compared different doses of vitamin C supplementation (500 mg vs. 1000 mg) and demonstrated greater protection to protein damage at higher dose [47].

In most of the included studies, the sample consisted only of males, which may indicate that the findings are mainly applicable to males, as it is highlighted in previous systematic review that evaluated the effects of antioxidant supplementation in muscle soreness [24]. However, gender had no relation with the effect of supplementation on lipid peroxidation immediately after exercise in our meta-regression. Likewise, the supplementation period was not related to the effect found, demonstrating that vitamin C supplementation over a long period of time does not show additional effects (Supplemental Fig. 2). This is due to the fact that 40 min after its oral ingestion, vitamin C is already bioavailable [52] and after 24 h its plasma concentration returns to basal levels [29].

The mechanical and metabolic stress, due to the transient state of imbalance between the pro and antioxidant systems during acute exercise, are responsible for muscle damage [53, 54]. Such damage is shown, among other forms, by the presence of intramuscular enzymes, mainly CK, in the blood plasma [55, 56], which shows the peak of its activity 24 h after the exercises [57]. As observed, vitamin C supplementation had no effect on CK at the evaluated moments, which may be justified in partly by the half-life of the antioxidant [29].

There is an inflammatory response [56] associated with muscle damage, which involves the release of cytokines, such as tumor necrosis factor-α (TNFα) and IL-6, in order to repair damaged tissue [53]. Vitamin C supplementation reduced IL-6 levels shortly after exercise, a probable

reflection of the reduction of oxidative stress parameters immediately after exercise, with a consequent delay in the signaling of the inflammatory response [7]. Inflammation and muscle damage are clinically manifested by muscle soreness and decreased muscle function, especially strength [7, 10]. This review demonstrates that muscle soreness and strength are not altered by vitamin C supplementation in healthy adults. However, individuals with low concentrations of vitamin C or hypovitaminosis it seems benefit most from supplementation of this antioxidant [58], as vitamin C has already been shown to be more effective in increasing exercise performance in individuals with low initial concentrations of vitamin C [59].

The present meta-analysis reinforces the hypothesis that supplementation with antioxidants interferes in exercise-induced redox signaling [50, 60]. The reduction of lipid peroxidation and IL-6, immediately after exercise in the group supplemented with vitamin C, demonstrate attenuation of the production of reactive species and delayed inflammation and, consequently, cell signaling [50]. Based on the results found, during sports competitions, vitamin C supplementation may be adopted by athletes as a strategy to aid in the recovery after exercise and, in the case of beginners in sports, this supplementation may help in the adaptation and continuity of regular physical exercise practice. However, it is important not to extrapolate these results to the context of exercise/training programs, since the repeated activation on signaling by transient increases in reactive species production, inflammatory response and muscle damage from each exercise session are necessary for muscle adaptation and remodeling [17, 61, 62]. Also, antioxidant supplementation can negatively interfere on muscle remodeling, besides showing risks for hypervitaminosis [63].

No included study presented a high risk of bias according to the Cochrane risk of bias tool [26], although the method used to generate the random sequence and allocation blinding was not clearly reported. Hence, it is suggested that further RCTs need to improve the methodological transparency. The quality of the evidence was evaluated through observations on the risk of bias, indirectness, inconsistency (heterogeneity), imprecision and publication bias, combined by GRADE [30, 31]. As found in previous systematic review [24], the quality of evidence ranged from very low to moderate, which indicates the need for further studies so that the true effect is estimated.

The present study has some limitations. First, the findings must not be generalized beyond the healthy population and are restricted to the effects of supplementation on acute exercises. Second, we have found important heterogeneities, that due the small number of studies in each outcome, we could not explore. For example, we could not determine the effects of different dosage, supplementation time, different exercise modalities (aerobic and anaerobic), and populations (athletes, active individuals, and untrained), for all outcomes. In the present systematic review, by investigating the effects of vitamin C supplementation on variables related to musculoskeletal functionality, it was only possible to evaluate muscle strength, indicating the need of further RCTs that evaluate the effects of this supplementation on functional variables in this condition.

Conclusion

This systematic review and meta-analyses show that vitamin C supplementation reduces oxidative stress (lipid peroxidation) and the inflammatory response (IL-6) after acute physical exercise in healthy volunteers, although with small and moderate size effects. However, such intervention does not reduce plasmatic levels of CK, CRP, cortisol or muscle soreness, nor improve muscle strength. In practice, vitamin C supplementation may be considered as an option to favor the recovery after exercises and/or intense physical activities, especially during sports competitions and for beginners in physical exercise programs.

Acknowledgements The authors thank the Postgraduate Program in Functional Rehabilitation. We would also like to thank the authors who kindly provided additional information needed for the analysis.

Funding This study was financed in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior—Brasil (CAPES)—Finance Code 001 and the Foundation for Research Support of the State of Rio Grande do Sul—FAPERGS—Public Notice 05/2017—Master.

Compliance with ethical standards

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

References

1. Egan B, Zierath JR (2013) Exercise metabolism and the molecular regulation of skeletal muscle adaptation. Cell Metab 17:162–184. https://doi.org/10.1016/j.cmet.2012.12.012
2. Heinonen I, Kalliokoski KK, Hannukainen JC et al (2014) Organ-specific physiological responses to acute physical exercise and long-term training in humans. Physiology 29:421–436. https://doi.org/10.1152/physiol.00067.2013
3. Schuch FB, Vancampfort D, Firth J et al (2018) Physical activity and incident depression: a meta-analysis of prospective cohort studies. Am J Psychiatry 175:631–648. https://doi.org/10.1176/appi.ajp.2018.17111194
4. Schuch FB, Stubbs B, Meyer J et al (2019) Physical activity protects from incident anxiety: a meta-analysis of prospective cohort studies. Depress Anxiety. https://doi.org/10.1002/da.22915
5. Pedersen BK, Saltin B (2015) Exercise as medicine—evidence for prescribing exercise as therapy in 26 different chronic diseases.

Scand J Med Sci Sports 25:1–72. https://doi.org/10.1111/sms.12581
6. Garber CE, Blissmer B, Deschenes MR et al (2011) American College of Sports Medicine. Quantity and quality of exercise for developing and maintaining neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. Med Sci Sport Exerc 43:1334–1359. https://doi.org/10.1249/MSS.0b013e318213fefb
7. Powers SK, Nelson WB, Hudson MB (2011) Exercise-induced oxidative stress in humans: cause and consequences. Free Radic Biol Med 51:942–950. https://doi.org/10.1016/j.freeradbiomed.2010.12.009
8. Teixeira ADO, da Silva Paulitsch F, Umpierre MDM et al (2014) Inflammatory response after session of resistance exercises in untrained volunteers. Acta Sci 37:31–39. https://doi.org/10.4025/actascihealthsci.v37i1.24149
9. Smith LL (2000) Cytokine hypothesis of overtraining: a physiological adaptation to excessive stress? Med Sci Sports Exerc 32:317–331. https://doi.org/10.1097/00005768-200002000-00011
10. Powers SK, Jackson MJ (2008) Exercise-induced oxidative stress: cellular mechanisms and impact on muscle force production. Physiol Rev 88:1243–1276. https://doi.org/10.1152/physrev.00031.2007.Exercise-Induced
11. Magal M, Dumke CL, Urbiztondo ZG et al (2010) Relationship between serum creatine kinase activity following exercise-induced muscle damage and muscle fibre composition. J Sports Sci 28:257–266. https://doi.org/10.1080/02640410903440892
12. Cheung K, Hume PA, Maxwell L (2003) Delayed onset muscle soreness treatment strategies and performance factors karoline. Sport Med 33:145–164
13. Peternelj T-T, Coombes JS (2011) Antioxidant supplementation during exercise training: beneficial or detrimental? Sport Med 41:1043–1069. https://doi.org/10.2165/11594400-000000000-00000
14. Howatson G, van Someren KA (2008) The prevention and treatment of exercise-induced muscle damage. Sport Med 38:483–503. https://doi.org/10.2165/00007256-200838060-00004
15. Yavari A, Javadi M, Mirmiran P, Bahadoran Z (2015) Exercise-induced oxidative stress and dietary antioxidants. Asian J Sports Med 6:e24898. https://doi.org/10.5812/asjsm.24898
16. Kawamura T, Muraoka I (2018) Exercise-induced oxidative stress and the effects of antioxidant intake from a physiological viewpoint. Antioxidants 7:119. https://doi.org/10.3390/antiox7090119
17. Coffey VG, Hawley JA (2007) The molecular bases of training adaptation. Sport Med 37:737–763
18. Poulab E, Sajedinia H, Hafezi F et al (2015) The effect of a four-week acute vitamin C supplementation on the markers of oxidative stress and inflammation following eccentric exercise in active men. Int J Basic Sci Appl Res 4:190–195
19. Davison G, Gleeson M (2007) The effects of acute vitamin C supplementation on cortisol, interleukin-6, and neutrophil responses to prolonged cycling exercise. Eur J Sport Sci 7:15–25. https://doi.org/10.1080/17461390701197734
20. Thompson D, Williams C, McGregor SJ et al (2001) Prolonged vitamin C supplementation and recovery from demanding exercise. Int J Sport Nutr Exerc Metab 11:466–481
21. Bohlooli S, Rahmani-Nia F, Babaei P, Nakhostin-Roohi B (2012) Influence of vitamin C moderate dose supplementation on exercise-induced lipid peroxidation, muscle damage and inflammation. Med dello Sport 65:187–197
22. Urso ML, Clarkson PM (2003) Oxidative stress, exercise, and antioxidant supplementation. Toxicology 189:41–54. https://doi.org/10.1016/S0300-483X(03)00151-3
23. Candia-luján R, Fernández JADP, Moreira OC (2015) ¿Son efectivos los suplementos antioxidantes en la disminución del dolor muscular tardío? Una revisión sistemática. Nutr Hosp 31:32–45. https://doi.org/10.3305/nh.2015.31.1.8171
24. Ranchordas MK, Rogerson D, Soltani H, Costello JT (2018) Antioxidants for preventing and reducing muscle soreness after exercise: a Cochrane systematic review. Br J Sports Med. https://doi.org/10.1136/bjsports-2018-099599
25. Moher D, Liberati A, Tetzlaff J et al (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 6:e1000097. https://doi.org/10.1371/journal.pmed.1000097
26. Higgins JPT, Green S (eds) (2011) Cochrane handbook for systematic reviews of interventions version 5.1.0 [updated March 2011]. Cochrane Collab. https://www.handbook.cochrane.org
27. Haynes RB, Mckibbon KA, Wilczynski NL et al (2005) Optimal search strategies for retrieving scientifically strong studies of treatment from Medline: analytical survey. BMJ 13:2–7. https://doi.org/10.1136/bmj.38446.498542.8F
28. Araújo CGS, Scharhag J (2016) Athlete: a working definition for medical and health sciences research. Scand J Med Sci Sport 26:4–7. https://doi.org/10.1111/sms.12632
29. Levine M, Padayatty SJ, Espey MG (2011) Vitamin C: a concentration-function approach yields pharmacology and therapeutic discoveries. Adv Nutr 2:78–88. https://doi.org/10.3945/an.110.000109.78
30. Balshem H, Helfand M, Schünemann HJ et al (2011) GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol 64:401–406. https://doi.org/10.1016/j.jclinepi.2010.07.015
31. GRADEpro GDT (2015) GRADEpro guideline development tool [software]. McMaster University (developed by Evidence Prime, Inc.). https://www.gradepro.org
32. Cohen J (ed) (1988) Statistical power analysis for the behavioral sciences, 2nd edn. San Diego
33. Higgins JPT, Thompson SG, Deeks JJ, Altman DG (2003) Measuring inconsistency in meta-analyses. Br Med J 327:557–560
34. Egger M, Smith GD, Schneider M, Minder C (1997) Bias in meta-analysis detected by a simple, graphical test. BMJ 315:629
35. Duval S, Tweedie R (2000) Trim and Fill: a simple funnel-plot–based method of testing and adjusting for publication bias in meta-analysis. Biometrics 56:455–463
36. Close GL, Ashton T, Cable T et al (2006) Ascorbic acid supplementation does not attenuate post-exercise muscle soreness following muscle-damaging exercise but may delay the recovery process. Br J Nutr 95:976–981. https://doi.org/10.1079/BJN20061732
37. Mizuma H, Tanaka M, Nozaki S et al (2009) Daily oral administration of crocetin attenuates physical fatigue in human subjects. Nutr Res 29:145–150. https://doi.org/10.1016/j.nutres.2009.02.003
38. Jakeman P, Maxwell S (1993) Effect of antioxidant vitamin supplementation on muscle function after eccentric exercise. Eur J Appl Physiol Occup Physiol 67:426–430. https://doi.org/10.1007/BF00376459
39. Bryer SC, Goldfarb AH (2006) Effect of high dose vitamin C supplementation on muscle soreness, damage, function, and oxidative stress to eccentric exercise. Int J Sport Nutr Exerc Metab 16:270–280. https://doi.org/10.1123/ijsnem.16.3.270
40. Karandish M, Rahideh ST, Moghaddam AZ (2008) Effect of vitamin C supplementation on oxidative stress markers following thirty minutes moderate intensity exercise in healthy young women. J Biol Sci 8:1333–1337
41. Vasankari T, Kujala U, Sarna S, Ahotupa M (1998) Effects of ascorbic acid and carbohygrate ingestion on exercise induced oxidative stress. J Sports Med Phys Fit 38:281–285
42. Alessio HM, Goldfarb AH, Cao G (1997) Exercise-induced oxidative stress before and after vitamin C supplementation. Int J Sport Nutr 7:1–9

43. Thompson D, Williams C, Kingsley M et al (2001) Muscle soreness and damage parameters after prolonged intermittent shuttle-running following acute vitamin C supplementation. Int J Sports Med 22:68–75
44. Thompson D, Bailey DM, Hill J et al (2004) Prolonged vitamin C supplementation and recovery from eccentric exercise. Eur J Appl Physiol 92:133–138. https://doi.org/10.1007/s00421-004-1064-y
45. Davison G, Gleeson M (2006) The effect of 2 weeks vitamin C supplementation on immunoendocrine responses to 2.5 h cycling exercise in man. Eur J Appl Physiol 97:454–461. https://doi.org/10.1007/s00421-006-0196-7
46. Connolly DAJ, Lauzon C, Agnew J et al (2006) The effects of vitamin C supplementation on symptoms of delayed onset muscle soreness. J Sports Med Phys Fit 46:462–467. https://doi.org/10.1249/00005768-200505001-01641
47. Goldfarb AH, Patrick SW, Bryer S, You T (2005) Vitamin C supplementation affects oxidative-stress blood markers in response to a 30-minute run at 75% VO_{2max}. Int J Sport Nutr Exerc Metab 15:279–290
48. Aguiló A, Monjo M, Moreno C et al (2014) Vitamin C supplementation does not influence plasma and blood mononuclear cell IL-6 and IL-10 levels after exercise. J Sports Sci 32:1659–1669. https://doi.org/10.1080/02640414.2014.912759
49. Yimcharoen M, Kittikunnathum S, Suknikorn C et al (2019) Effects of ascorbic acid supplementation on oxidative stress markers in healthy women following a single bout of exercise. J Int Soc Sports Nutr 16:1–9
50. Cobley JN, Mchardy H, Morton JP et al (2015) Influence of vitamin C and vitamin E on redox signaling: implications for exercise adaptations. Free Radic Biol Med J 84:65–76
51. Smirnoff N (2018) Free radical biology and medicine ascorbic acid metabolism and functions: a comparison of plants and mammals. Free Radic Biol Med J 122:116–129
52. Bates CJ, Jones KS, Bluck LJC (2004) Stable isotope-labelled vitamin C as a probe for vitamin C absorption by human subjects. Br J Nutr 91:699–705. https://doi.org/10.1079/BJN20041103
53. Tidball JG (2011) Mechanisms of muscle injury, repair, and regeneration. Compr Physiol 1:2029–2062. https://doi.org/10.1002/cphy.c100092
54. Tee JC, Bosch AN, Lambert MI (2007) Metabolic consequences of exercise-induced muscle damage. Sport Med 37:827–836. https://doi.org/10.2165/00007256-200737100-00001
55. Clarkson PM, Nosaka K, Braun B (1992) Muscle function after exercise-induced muscle damage and rapid adaptation. Med Sci Sports Exerc 24:512–520
56. Bessa AL, Oliveora VN, Agostini GG et al (2016) Exercise intensity and recovery: biomarkers of injury, inflammation, and oxidative stress. J Strength Cond Res 30:311–319
57. Noakes TD (1987) Effect of exercise on serum enzyme activities in humans. Sport Med 4:245–246
58. Margaritelis NV, Paschalis V, Theodorou AA et al (2018) Antioxidants in personalized nutrition and exercise. Adv Nutr 9:813–823
59. Paschalis V, Theodorou AA, Kyparos A et al (2016) Low vitamin C values are linked with decreased physical performance and increased oxidative stress: reversal by vitamin C supplementation. Eur J Nutr 55:45–53. https://doi.org/10.1007/s00394-014-0821-x
60. Margaritelis NV, Cobley JN, Paschalis V et al (2016) Principles for integrating reactive species into in vivo biological processes: examples from exercise physiology. Cell Signal 28:256–271
61. Cobley JN, Close GL, Bailey DM, Davison GW (2017) Redox biology exercise redox biochemistry: conceptual, methodological and technical recommendations. Redox Biol J 12:540–548
62. Owens DJ, Twist C, Cobley JN et al (2019) Exercise-induced muscle damage: what is it, what causes it and what are the nutritional solutions ? Eur J Sport Sci 19:71–85. https://doi.org/10.1080/17461391.2018.1505957
63. Nikolaidis MG, Kerksick CM, Lamprecht M, Mcanulty SR (2012) Does vitamin C and E supplementation impair the favorable adaptations of regular exercise? Oxid Med Cell Longev 2012:1–11. https://doi.org/10.1155/2012/707941