Antioxidants for preventing and reducing muscle soreness after exercise: a Cochrane systematic review

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Antioxidants for preventing and reducing muscle soreness after exercise: a Cochrane systematic review

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Abstract

Objective

To determine whether antioxidants supplements and antioxidant-enriched foods can prevent or reduce delayed onset muscle soreness after exercise.

Methods

We searched the Cochrane Bone, Joint and Muscle Trauma Group Specialised Register, the Cochrane Central Register of Controlled Trials, MEDLINE, Embase, SPORTDiscus, trial registers, reference lists of articles and conference proceedings up to February 2017

Results

In total, 50 studies were included in this review which included a total of 1089 participants (961 were male and 128 were female) with an age range between 16 and 55 years. All studies used an antioxidant dosage higher than the recommended daily amount. The majority of trials (47) had design features that carried a high risk of bias due to selective reporting and poorly described allocation concealment, potentially limiting the reliability of their findings. We rescaled to a 0 to 10 cm scale in order to quantify the actual difference between groups and we found that the 95% CIs for all five follow-up times were all well below the minimal important difference of 1.4 cm: up to 6 hours (MD -0.52, 95% CI -0.95 to -0.08); at 24 hours (MD -0.17, 95% CI -0.42 to 0.07); at 48 hours (MD -0.41, 95% CI -0.69 to -0.12); at 72 hours (MD -0.29, 95% CI -0.59 to 0.02); and at 96 hours (MD -0.03, 95% CI -0.43 to 0.37). Thus, the effect sizes suggesting less muscle soreness with

antioxidant supplementation were very unlikely to equate to meaningful or important differences in practice.

Conclusions

There is moderate to low-quality evidence that high dose antioxidant supplementation does not result in a clinically relevant reduction of muscle soreness after exercise at up to 6 hours or at 24, 48, 72 and 96 hours after exercise. There is no evidence available on subjective recovery and only limited evidence on the adverse effects of taking antioxidant supplements.

Introduction

Delayed onset muscle soreness (DOMS) typically occurs after strenuous and unaccustomed exercise and physical activity. It is classified as a grade 1 muscle strain injury and is characterised by localised tenderness and soreness.[1] Depending on the severity of exercise, DOMS typically peaks between 24 to 72 hours after a bout of exercise but eventually disappears after five to seven days.[2-7] DOMS could be detrimental for athletes who are returning to training from a prolonged period of inactivity. In addition, DOMS could deter individuals from adhering to an exercise programme. For some individuals, DOMS could result from excessive physical activity associated with daily living, particularly if repeated eccentric movements or unaccustomed physical activity are involved.

Several theories have been proposed to explain the mechanisms underlying DOMS. These include lactate accumulation,[8] inflammation,[9] muscle spasm,[10] muscle damage,[11] connective tissue damage,[12]and increased muscle temperature.[13] A common feature of several of these proposed mechanisms is an increased production of free radicals,[14] and reactive oxygen species. Indeed, it has been shown that reactive oxygen species are produced in nearly every biological process and that they also play a crucial role as signalling molecules for translating the exercise signals to appropriate adaptations.[15]

The rationale for taking antioxidant supplements after exercise to reduce DOMS comes from the notion that they could reduce the negative

effects of reactive oxygen species and oxidative stress resulting from exercise.[16] Oxidative stress could deplete the body's antioxidant defences and increase the rate of free radical production.[17-19] Moreover, unaccustomed, eccentric and exhaustive exercise may also induce inflammatory reactions which can contribute to increased reactive oxygen species production and reduced antioxidant defences.[20] These can cause exercise-induced muscle damage and result in DOMS.[1] Dietary antioxidants may counteract oxidative stress by reducing the production of free radical and reactive oxygen species associated with exercise.[17] Reducing DOMS could be beneficial to athletes when returning to training from injury (i.e. after a period of inactivity), and it could help sedentary and older individuals recover from unaccustomed physical activity.

The ease of taking antioxidant supplements to prevent and reduce muscle soreness after exercise and enhance recovery makes it an attractive option for physically active individuals. Moreover, antioxidant supplements are available to buy from supermarkets and health food stores and some are marketed to enhance recovery. Despite the popularity of antioxidant supplements, the evidence supporting its used is mixed.[21-23] Therefore, the objective of this systematic review was to determine whether antioxidant supplements and antioxidant-enriched foods could prevent or reduce DOMS after exercise.

Methods

Inclusion criteria

Any randomised controlled trials or quasi-randomised controlled trials investigating the effects of dietary antioxidants on preventing or reducing delayed onset muscle soreness were considered for this meta-analysis.

Search strategy

A systematic search of the literature was conducted in the Cochrane Bone, Joint and Muscle Trauma Group Specialised Register, the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase and SPORTDiscus, current to February 2017 was performed by two authors. ClinicalTrials.gov and the World Health Organization Clinical Trials Registry Platform were also searched for any ongoing or recently completed studies. Experts in the field were also contacted to find unpublished trials. The reference list of all included studies and relevant reviews were also screened for further references to relevant trials. No language restrictions were applied.

Data extraction

Two authors independently extracted data using a customised form. We resolved any disagreements by consultation with the other authors. In

some cases, the primary authors of selected studies were contacted for additional information and data.

Heterogeneity and risk of bias

For all included studies, methodologic quality was assessed by two authors independently, using the Cochrane risk of bias tool.[24] We resolved any disagreement by discussion and, if necessary, consultation with the other authors. Heterogeneity was assessed using the Chi^2 test and I^2 statistic, with the level of significance for the Chi^2 test being set at $P = 0.1$.[25] We interpreted values of I^2 as follows: might not be important (0% to 40%); may represent moderate heterogeneity (30% to 60%); may represent substantial heterogeneity (50% to 90%); and may represent considerable heterogeneity (75% to 100%).

Meta-analyses

Mean differences with 95% confidence intervals were calculated for continuous data using RevMan (Review Manager; RevMan). When studies used different ways of measuring a continuous outcome standardised mean differences and 95% confidence intervals were calculated. Due to substantial clinical and statistically significant heterogeneity a random-effects model, again with 95% confidence intervals, was employed.

Subgroup analyses

Subgroup analyses were performed in RevMan. Subgroup analyses included the timing of anti-oxidant administration (pre-exercise versus post-exercise), type of exercise (mechanically induced damage versus whole body aerobic exercise), and funding source (trials funded by food company or provider of antioxidant supplements versus those not funded by food company or provider of antioxidant supplements).

Results

Study Characteristics

We completed the search in February 2017 and 1558 records from the following databases were screened: Cochrane Bone, Joint and Muscle Trauma Group Specialised Register (25 records), CENTRAL (194),MEDLINE (302), Embase (476), SPORTDiscus (117), ClinicalTrials.gov (162) and the WHO International Clinical Trials Registry Platform (282). We also identified 12 potentially eligible studies from ongoing searches and through contacting experts in the field. The search resulted in the identification of 128 potentially eligible studies, for which we obtained full reports. Upon study selection, we included 50 and excluded 77.

The 50 trials included in this systematic review had a total of 1089 participants with 901 participants in the parallel-group trials (range 7 to 54) and 188 participants in the cross-over trials (range 8 to 24). All 50 studies were randomised controlled trials; no quasi-randomised controlled trials met the inclusion criteria. Thirty-eight trials (with a total of 901 participants) employed a parallel design.[21,22,26-59] The other 12 trials (with a total of 188 participants) employed a cross-over design. [60-71]

Seven trials were designed to produce DOMS under field-based conditions,[22,34,43-45,63] and the other 43 studies were designed to produce DOMS under laboratory-based conditions. In all trials, an antioxidant supplement was compared with a placebo. Thirteen trials used antioxidants from a whole natural food source, [22,28,29,40,43,45,50,61,63,64,67,70,71] 19 used an

antioxidant extract or mixed antioxidants,[26,31,34,36,37,39,41,42,44,47,48,51,52,54,60,65,66,68] and 18 provided either vitamin C or vitamin E or both together.[21,27,30,32,33,35,38,46,49,53,55,57-59,62,69,72,73] All studies used a placebo either as a powder, capsule or drink; however, three studies did not provide details of what the placebo comprised.[46,49,60] No trials compared high-dose versus low-dose antioxidant supplements, where the low-dose supplementation is within normal or recommended levels for the antioxidant involved.

There was a large variation across the studies regarding the duration of supplementation: the shortest period was under one day[68,69] and the longest period was 91 days.[39] Although the form of supplement was varied, including capsules, powders and drinks, every study used an antioxidant dosage higher than the recommended daily amount. Every study required the participant to ingest the supplement orally either once daily or up to three times per day. Supplementation was taken before, the day of and after exercise for up to several days in all the studies except for three studies where supplements were post-exercise only.[65,67,74]

Funding

In all, 21 studies were industry funded either by a food company or a provider of antioxidant supplements. [26-29,31,32,39,41,43,47,50,52,58,60,61,67-71,73] Of the 28 other studies reporting on funding, 15 declared “none” in their report;[21,30,33-36,40,44,46,49,53,57,59,62] the other 13 referring to various sources of university and public body research funding sources.[22,37,38,42,45,48,51,54,55,63-66]

We were unsuccessful in obtaining information on funding from the only trial that did not report on this.[56]

Risk of Bias

Forty-seven trials (94%) had design features that were deemed to carry a high risk of bias due to random sequence generation (19 trials),[21,22,27,35,37,41-43,46,49,52,56,57,60,61,65,66,70,71] selective reporting (41 trials),[21,22,26-33,35-40,42,46-49,51,53-63,66-73] poorly described allocation concealment (30 trials),[21,22,27,35-37,40,42,43,45-47,49,51-53,56,58-62,64,65,68-73] attrition bias (12 trials),[32,40,42,45,47,52,54,55,60-62,65] and lack of dietary monitoring during the intervention (16 trials),[26,29,31,42,46,49,53-55,57,59,63-66,69] potentially limiting the reliability of their findings.

Primary Outcomes

All of the 50 trials included in this review measured muscle soreness, however, there were differences in the types of soreness scales used. Thirty-three trials measured muscle soreness using a 0 to 10 cm (or 0 to 100 mm) visual analogue scale (VAS). Of the 17 other trials, seven[65,75-80] measured soreness using a 1 to 10 cm scale; four trials[29,45,81,82] used the 0 to 20 cm (or 0 to 200 mm) scale; two studies[38,48] used a 0- to 6-point scale, Herrlinger[39] used a 0 to 7 Likert scale, Drobnic[36] used a 0- to 4-point scale; Cobley[34] used a 0 to 12 cm scale and Su[56] used the Borg CR-10 scale. The Borg CR-10 scale ranges from 0 (no soreness) to 10 (maximal soreness). In the included studies, participants were asked to rate muscle soreness on the soreness scales by either carrying out a squat using body weight, self-palpitation of muscle or based on muscle soreness at rest.

Forty-eight studies presented data on muscle soreness at various different time points based on various visual analogue scale (VAS) scores. Results are presented at eight follow-up times after exercise: up to 6 hours, and at 24, 48, 73, 96, 120, 144 and 168 hours.

Antioxidant supplementation reduced muscle soreness in comparison to the placebo condition when measured up to 6 hours post-exercise (standardised mean difference (SMD) -0.30, 95% confidence interval (CI) -0.56 to -0.04; participants = 525; studies = 21; I^2 = 53%; low-quality evidence); at 24 hours after exercise (SMD -0.13, 95% CI -0.27 to 0.00; participants = 936; studies = 41; I^2 = 5%; moderate-quality evidence); at 48 hours after exercise (SMD -0.24, 95% CI - 0.42 to -0.07; participants = 1047; studies = 45; I^2 = 47%; low quality evidence); and at 72 hours after exercise (SMD -0.19, 95% CI -0.38 to -0.00; participants = 657; studies = 28; I^2 = 27%; moderate-quality evidence). There was little effect of antioxidants on muscle soreness at 96 hours after exercise (SMD -0.05, 95% CI -0.29 to 0.19; participants = 436; studies = 17; I^2 = 31%; low-quality evidence). Far fewer trials provided data at five days or subsequently. There was very low-quality evidence of little effect of antioxidants on muscle soreness at 120 hours (SMD 0.21, 95% CI -0.26 to 0.69; participants = 128; studies = 4; I^2 = 39%), at 144 hours (SMD -0.23, 95% CI -1.11 to 0.65; participants = 20; studies = 1) or at 168 hours (SMD - 0.04, 95% CI -0.48 to 0.41; participants = 80; studies = 4; I^2 = 0%).

As there was considerable variation in the units used to measure muscle soreness, we rescaled all trials to the 0 to 10 scale at the first five time points in order to explore the actual difference between groups on a

standard scale. The results are as follows: up to 6 hours (mean difference (MD) -0.52, 95%CI -0.95 to -0.08; participants = 525; studies = 21; I^2 = 66%); at 24 hours (MD - 0.17, 95% CI -0.42 to 0.07; participants = 936; studies = 41; I^2 = 29%); at 48 hours (MD -0.41, 95% CI -0.69 to - 0.12; participants = 1047; studies = 45; I^2 = 64%); at 72 hours (MD -0.29, 95% CI -0.59 to 0.02; participants = 657; studies = 28; I^2 = 27%); and at 96 hours (MD-0.03, 95% CI -0.43 to 0.37; participants = 436; studies = 17; I^2 = 51%). This rescaling also allows us to examine whether the antioxidant supplement produces a clinically important difference. For consistency with Bleakley,[4] we considered 1.4 cm as the minimal important difference (MID) for pain reduction on a 10 cm visual analogue scale; this was based on an estimated MID for musculoskeletal conditions of the shoulder by Tashjian.[83] It is notable that all of the upper limits of the 95% CIs of these five analyses are lower than this MID and hence all quantitative differences do not appear to represent person-relevant differences in muscle soreness.

Subgroup and sensitivity analyses

We performed only a few subgroup and sensitivity analyses. We selected the 24 and 48 hours analyses for subgroup analyses given that these were the categories with the largest number of trials. We did not use the up to 6 hours time period because of the variation in the timing of measurement: i.e. some studies measured this outcome immediately after exercise whereas other studies measured this up to 2 hours or up to 6 hours after exercise. A sensitivity analysis exploring the use of the fixed-effect model for all eight follow-up times produced similar results to that of random-effects model. A subgroup analysis could not be performed on

timing of administration (i.e. pre-exercise and post-exercise versus post-exercise only) because there were very few trials (one or two studies depending on the time of follow-up) in the post-exercise group. We performed a subgroup analysis on the type of exercise, that is, mechanically induced versus whole body aerobic exercise for the 24 and 48 hour follow-up times. There is no evidence of subgroup differences for muscle soreness for type of exercise at 24 hours ($Chi^2 = 0.44$, df = 1; P = 0.51, $I^2 = 0\%$) or at 48 hours ($Chi^2 = 0.88$, df = 1; P = 0.35, $I^2 = 0\%$). Our second subgroup analysis was based on source of funding where we compared studies that were funded by a food company or provider of antioxidant supplements versus studies that there were not. There is no evidence of subgroup differences for muscle soreness according to source of funding at 24 hours ($Chi^2 = 0.03$, df = 1, P = 0.87, $I^2 = 0\%$) or 48 hours ($Chi^2 = 0.10$, df = 1, P = 0.875 $I^2 = 0\%$); no information on funding was available for Su.[56]

We conducted a sensitivity analysis testing trials at unclear risk of bias, relating to random sequence generation, allocation concealment or both, which included 19 trials.[22,26,28-34,38,39,44,48,50,54,55,63,67,68] This analysis made little difference to the overall effect at either 24 hours post-exercise (SMD -0.10, 95% CI -0.37 to 0.17; participants = 280; studies = 14; $I^2 = 19\%$) or at 48 hours (SMD -0.31, 95% CI -0.66 to 0.04; participants = 327; studies = 16; $I^2 = 57\%$).

Subjective Recovery

No study measured subjective recovery (return to previous activities without signs or symptoms).

Adverse effects

Nine studies[34,41,43-45,50,52,64,65] reporting on a total of 216 participants, reported on this outcome (very low-quality evidence). One study reported that all six participants in the NAC (N-acetylcysteine) supplementation group had diarrhoea, which was mild in five participants and severe diarrhoea in one.[34] The same study reported mild indigestion in four participants (67%) in the NAC group and one of six participants in the placebo group. Another study[43] reported that tart cherry juice caused mild gastrointestinal distress in one of 26 participants taking the antioxidant supplement. Seven studies reported no adverse effects of taking the antioxidant supplementation.[41,44,45,50,52,64,65] The remaining 41 studies failed to report adverse effects.

Discussion

This review examined the effectiveness of antioxidants for preventing and treating muscle soreness after exercise. Fifty randomised placebo-controlled studies were included, 12 of which used a crossover design. The 50 studies involved a total of 1089 participants (961 male; 128 female; age range 16 to 55 years). The studies were heterogeneous, including the timing (pre-exercise or post exercise), frequency, dose or duration, and type of antioxidant supplementation, and the type of preceding delayed onset muscle soreness (DOMS)-producing exercise. All studies used an antioxidant dosage higher than the recommended daily amount. No studies compared high-dose versus low-dose, where the low-dose supplementation was within normal or recommended levels for the antioxidant involved.

Pooled standardised mean difference (SMD) results for muscle soreness indicated a small difference in favour of antioxidant supplementation after DOMS-inducing exercise at all main follow ups (up to 6 hours; low-quality evidence, at 24 hours; moderate-quality evidence, at 48 hours; low-quality evidence, at 72 hours; moderate- quality evidence, at 96 hours; low-quality evidence. When, however, we rescaled all the trial results to the 0 to 10 cm scale in order to compare the actual difference between groups, we found that the 95% confidence intervals (CIs) for all five follow up times were all below 1.0 cm, and thus all below the minimal important difference of 1.4 cm that we used in this review. Thus, all statistical differences in DOMS favouring antioxidant supplementation were unlikely to equate to meaningful or important differences in practice.

316 Neither of our subgroup analyses to examine for differences in
317 effect according to type of DOMS-inducing exercise (mechanical versus
318 whole body aerobic) or according to funding source confirmed subgroup
319 differences. Sensitivity analyses to test the selection of the statistical model
320 for pooling (fixed-effect instead of random effects) and the exclusion of
321 cross-over studies all showed similar results to the main analyses. None of
322 the 50 studies reported on subjective recovery (return to previous activities
323 without signs or symptoms). Only nine studies (216 participants) reported
324 on adverse effects, with actual events reported in two studies. One study[34]
325 (12 participants) reported that all six participants in the NAC (N-
326 acetylcysteine supplementation group had diarrhoea, which was mild in
327 five participants and severe in one. The same study[34] reported mild
328 indigestion in four participants (67%) in the NAC group and one of six
329 participants in the placebo group. It should be noted that NAC
330 supplementation is usually prescribed and it has been found to cause
331 uncomfortable side effects including nausea and diarrhoea in other studies.
332 Another study[43] reported that tart cherry juice caused mild gastrointestinal
333 distress in one of 26 participants taking the antioxidant supplement. The
334 other seven studies reported no adverse effects of taking the antioxidant
335 supplementation; this included 10 participants having NAC
336 supplementation in one study. Overall, the available evidence for adverse
337 events is very low-quality.
338
339 The majority of the 1089 participants included in this review were
340 male (961; 88.2%) and so arguably the findings of the review are mainly
341 applicable to males but there is no biological basis for why antioxidants
342 should have a different effect in the two sexes. These sex differences are

typical of what is observed in the athletic recovery literature.[3,4,7] More noteworthy is that no data from highly-trained elite athletes were included in the analyses; the data pertaining to nine elite athletes tested in McCormick[63] were not included in the meta-analyses because the exercise paradigm was completely different to all the other studies included in this review. As the majority of the participants were either college students or relatively young and active, these findings cannot be generalised in the elite athlete population who have a different physiological and training status. Some reservations in terms of applicability also apply to older individuals due to their anatomical and physiological characteristics as there were no older participants included in this review (age range of participants: 16 to 55 years).

We assessed the quality of evidence using the GRADE framework, which combines considerations of risk of bias, indirectness, inconsistency (heterogeneity), imprecision and publication bias. We downgraded all outcomes one level for serious risk of bias, due mainly to selective reporting bias (the majority of the trials failed to report on adverse effects) and, to a lesser degree, attrition biases. We did not downgrade for indirectness in relation to muscle soreness. We downgraded two outcomes for serious inconsistency reflecting heterogeneity that could not be traced to the inclusion of just one outlier trial. Pooled evidence did not support downgrading for imprecision. Our tests for publication bias did not reveal a serious concern, although all were small studies. Thus, we did not downgrade for publication bias. We concluded that the quality of the evidence ranged from moderate to very low.

It is important to acknowledge some important limitations of this review. Firstly, data from 14 studies[21,27,35,37,42,47,52,56,60,61,65,67,70,71] were extracted from graphs using Graphclick 2010 Arizona (version 3.0.2, 2010) because the authors did not respond to several emails requested mean and SD data. Whilst this is not ideal, we tried to minimise error by having two review authors (MR and DR) independently extract the data, with any discrepancies resolved by consultation with the third and fourth authors (HS and JC). Secondly, our inclusion of cross-over studies and our analysis of their data as if from a parallel group trial, thus without adjustment for the cross-over design, are other potential sources of bias. With one exception, the cross-over studies included in this review used a washout period of two to six weeks, which is sufficient to allow the muscles to recover. The exception[60] used a washout period of only five days between treatments and therefore carries some risk of a carry-over effect; sensitivity analysis to check on the effect of excluding the data from this trial did not result in important changes. Further sensitivity analyses checking the effects of excluding the cross-over trials from the muscle soreness analyses showed that our inclusion and handling of the cross-over studies did not have an important impact on the review results.

Conclusions

There is moderate- to low-quality evidence that antioxidant supplementation does not result in a clinically relevant reduction of DOMS after exercise at any of the five follow-up times assessed (up to 6 hours and at 24, 48, 72 and 96 hours after exercise. There is no evidence available on

subjective recovery and only limited evidence on adverse effects of taking antioxidant supplements. Some antioxidant supplements such as N-acetylcysteine may cause unwanted side effects including gastrointestinal discomfort and diarrhoea. Thus, taking antioxidants supplements and antioxidant-enriched foods is not an effective strategy to reduce DOMS after exercise.

What is already known?

Taking antioxidants supplements to reduce muscle soreness is a common strategy used by recreational and elite athletes. However, little is known about how effective antioxidants are at reducing delayed onset muscle soreness.

What are the new findings?

- There is moderate to low-quality evidence that high dose antioxidant supplementation does not result in a clinically relevant reduction of muscle soreness after exercise at up to 6 hours or at 24, 48, 72 and 96 hours after exercise.
- There is no evidence available on subjective recovery and only limited evidence on the adverse effects of taking antioxidant supplements.
- The findings of, and messages from, this review provide an opportunity for researchers and other stakeholders to come together and consider what are the priorities, and underlying justifications, for future research in this area.

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Contributorship

Mayur Ranchordas identified the research idea for the review, wrote the protocol, extracted the data, wrote the review and is the guarantor.

David Rogerson assisted with drafting the protocol and data extraction.

Hora Soltani provided feedback on the draft protocol and review.

Joseph Costello assisted with data analysis and drafted the final review.

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Mayur Ranchordas co-authored one of the included studies (Lynn 2015). Decisions on inclusion of this study, the 'Risk of bias'

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