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Effects of vitamin D supplementation on muscle function and recovery after exercise-induced muscle damage: a systematic review.

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Author contributions

The study was designed by the two authors. Conceptualization, investigation, methodology, study selection, data extraction, data interpretation, writing, editing, and preparation of the manuscript were also undertaken by the two authors. Both authors reviewed and approved the final version of the article.

This manuscript does not use language that is stigmatizing or prejudiced when referring to study participants.

Author biographies

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Key points

- Regular Vitamin D supplementation may be a good recovery strategy from strenuous exercise.
- Supplementation is effective with a minimum dose of 2000 IU/day for periods of more than one week.
- Athletes may also benefit from ingesting a single dose before exercise, but further research is needed.

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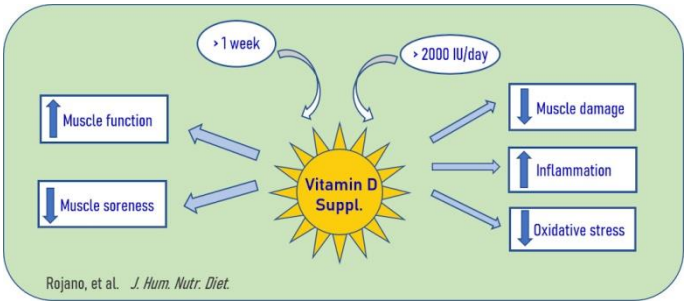
ABSTRACT

Background: Vitamin D is essential for the optimal health of the skeletal system. However, this vitamin is also involved in other functions of the human body, such as muscle, immune and inflammatory ones. Some studies suggest that adequate levels of vitamin D support muscular function during exercise and accelerate recovery because they reduce specific pro-inflammatory cytokine levels, but those results have not always been observed. Therefore, this review aims to evaluate the effects of vitamin D supplementation on inflammation, oxidative stress and recovery after exercise. **Methods:** This systematic review was conducted using the PRISMA guidelines. A literature search of SPORTDiscuss, PubMed, Web of Science and Scopus was performed from inception through February, 2021. The articles' methodological quality was assessed with the PEDro scale. **Results:** After the application of the inclusion and exclusion criteria, 11 eligible articles were included. All the studies were considered of moderate methodological quality. Ten studies involved regular vitamin D supplementation for more than 7 days, and one study performed acute vitamin D supplementation 24 h before exercise. **Conclusions:** The existing evidence suggests that vitamin D supplementation for periods of more than 1 week with a minimum dose of 2000 IU/day appears to be an efficacious strategy for attenuating muscle damage and inflammation after exercise. The potential positive effects on muscle function, muscle pain and oxidative stress need to be confirmed with new investigations. Further research is also required to clarify the adequate vitamin D dosage to obtain positive effects without adverse effects.

Graphical Abstract

Vitamin D and Recovery after Exercise-Induced Muscle Damage



Keywords: vitamin D, inflammation, oxidative stress, muscle damage, muscle soreness, recovery.

INTRODUCTION

A free radical is an atom or molecule with one or more unpaired electrons in its valency shell. This structure makes the atom or molecule unstable and highly reactive.[1] Free radicals are the products of cellular metabolism and they are generated in the mitochondria when oxygen is used to produce ATP.[2] Among the most important free radicals generated in living cells are those derived from oxygen, referred to as reactive oxygen species (ROS).[2,3] At low or moderate levels, ROS exert beneficial effects in cells, serving as molecular signals, which activate stress responses beneficial to the organism.[4] However, at high concentrations, if they cannot be neutralized by the endogen antioxidant system, they generate a condition termed oxidative stress, which can cause severe damage to cell structures.[2,5]

Strenuous and prolonged muscular exercise, particularly after eccentric muscle actions, produce muscle damage and lead to an increase in ROS production that occurs primarily in skeletal muscles and generates oxidative stress, which negatively impacts exercise performance.[6,7] An optimum level of ROS is necessary for muscle fibres to generate 100% of their maximal isometric force production,[8] but any deviation from that optimal redox state decreases the muscles' ability to generate force.[8,9]

The human body has an endogen antioxidant system, which, together with the exogenous antioxidants consumed through the diet, are responsible for the elimination of ROS, maintaining the necessary redox balance.[5] Therefore, supplementation with antioxidant and anti-inflammatory substances may attenuate inflammation and oxidative stress, enhancing the recovery of muscle function after exercise,[10] which becomes particularly important for elite athletes.

Ibuprofen and non-steroidal anti-inflammatory drugs have been traditionally used to reduce inflammation and DOMS,[11] but they have important gastrointestinal and cardiovascular adverse effects.[6] Hence, there is increasing interest in supplementation with natural antioxidant and anti-inflammatory foods, particularly polyphenol-rich foods, which have been associated with a range of health benefits.[12] Tart cherry, pomegranate or even green tea have been widely used in sports to accelerate muscle function recovery due to the antioxidant and anti-inflammatory properties of their phenolic compounds.[13-15]

Vitamin D is a fat-soluble vitamin that also appears to have anti-inflammatory and antioxidant properties.[16] It is considered a vitamin because small amounts of it are necessary for good human health. However, it is, in fact, a hormone because the required amount can be produced in the human body when the skin is exposed to ultraviolet solar radiation.[17,18] Its primary function is to regulate bone metabolism and calcium and phosphate absorption, which are necessary for bone mineralization and growth.[19,20] However, recent investigations have determined that this vitamin is also involved in other functions, such as muscular, inflammatory and immune ones, and may enhance sports performance.[21-23] At present, vitamin D supplementation is considered to be potentially protective from unfavourable COVID – 19 outcomes.[24]

Although it is not known whether vitamin D has a direct impact on muscle function,[25] vitamin D receptors have been identified in muscle cells, which supports the idea of a direct impact on muscle contraction.[26] It has been suggested that vitamin D deficiency may affect the muscles' capacity for recovery after exercise.[27] Vitamin D has anti-inflammatory properties[28] because it down-regulates the synthesis of specific pro-inflammatory cytokines.[29] In fact, according to Choi et al.,[30] exercise-induced inflammation is significantly reduced in rats after vitamin D supplementation.

The two major physiologically relevant forms of vitamin D are vitamin D2 (ergocalciferol) and D3 (cholecalciferol).[28] The main source of vitamin D is endogenous production by the human body when it is exposed to sunlight.[18] Ultraviolet radiation converts 7-dehydrocholesterol present in the skin to vitamin D3.[31,32] In the liver, vitamin D3 is hydroxylated, generating 25(OH)D or calcidiol, and then it is further hydroxylated in the kidney to the active form 1,25(OH)2D or calcitriol.[33] Serum 25(OH)D has a half-life of 15 days, which makes it the best indicator of vitamin D levels in the human body.[34] Apart from endogenous production, the second source of vitamin D is the dietary intake, either as vitamins D2

or D3. Because it is fat soluble, its absorption improves when high-fat meals are consumed.[35]

The desirable levels of 25(OH)D required for good health are unknown. However, some authors recommend serum levels of 30–50 ng/mL. To that end, a daily intake of 600 international units (IU) for those aged less than 70 years and 800 IU for those 70 years or older is recommended.[36,37] However, other authors suggest that those quantities are not sufficient to obtain benefits in athletic performance.[16,38] With regard to human toxicity, according to Holick,[18] toxicity has not been associated with daily intakes of 10000 IU for periods of up to 5 months. More recently, Adebayo et al.[39] concluded in their review that none of the 3353 subjects included in the randomized-controlled trials analyzed reported any adverse effect with vitamin D doses of 200–7000 IU.

In humans, it has been reported that vitamin D contributes to optimal muscle function, even in physically inactive older people.[40] According to some authors,[41,42] adequate levels of vitamin D support muscle contraction during exercise and enhance muscle recovery due to the down-regulation of specific pro-inflammatory cytokines. Moreover, some studies suggest that vitamin D supplementation reduces exercise-induced muscle damage (EIMD).[30] Nonetheless, not all researches carrying out a vitamin D supplementation have observed significant reductions in inflammatory markers after exercise.[43,44]

Due to the contradictory results observed of the effects of vitamin D supplementation on muscle function and recovery after exercise and because we have not found any review on this subject, this systematic review aims to summarize the effects of vitamin D supplementation on muscle damage and recovery after EIMD in humans.

METHODS

The protocol for this systematic review was designed in accordance with the Preferred Reporting of Systematic Reviews and Meta-Analyses (PRISMA) statement,[45] and registered at PROSPERO (CRD42022321140). The two authors independently performed the literature search, the study selection, and the data extraction. Any disagreement was resolved by consensus.

Inclusion and exclusion criteria

The studies included in this systematic review fulfilled the following inclusion criteria: (i) research conducted with human participants, (ii) original articles in peer-

reviewed publications, (iii) original studies that had investigated only vitamin D supplementation on muscle damage and recovery after exercise, (iv) research conducted with one control/placebo group, and (v) articles published from inception to February 2022. Exclusion criteria were: (i) research conducted with animals, (ii) non-English articles, (iii) systematic reviews or meta-analyses, (iv) studies that underwent other interventions in addition to vitamin D supplementation, and (v) studies that reported results inadequately or without adequate statistical analysis.

Search strategy and data extraction

Four electronic databases were searched: SPORTDiscuss, PubMed, Web of Science and Scopus. The search was limited to publications in English and journal articles. The following search was performed: (vitamin d OR ergocalciferol OR cholecalciferol) (Title) AND (supplement*) (Title) AND (muscle damage OR oxidative stress OR recovery OR exercise OR muscle pain OR antioxidant OR inflammation OR soreness (Title)) AND (sports OR exercise OR physical activity OR training (all fields)). A manual search of the reference sections of selected articles was also made to identify additional relevant studies. The search strategy is depicted in Figure 1.

After applying inclusion and exclusion criteria the following data were extracted from each study: first author name, year of publication, the intervention and placebo group characteristics, dosage of supplements, supplementation duration, exercise protocol to induce muscle damage and the effects of supplementation on functional measures, muscle soreness and markers of muscle damage, inflammation and oxidative stress.

Methodological quality assessment

The methodological quality of the articles was assessed with the PEDro scale, which is based on the Delphi list developed by Verhagen et al.[46] and is a reliable and objective tool that helps identify which studies are likely to be externally valid (criterion 1), internally valid (criteria 2–9) and could have sufficient statistical information to make their results interpretable (criteria 10 and 11).[13] Points are only awarded when a criterion is clearly satisfied, and criterion one, which relates to external validity, is not used to calculate the PEDro score. A score of 9–10 on the PEDro scale was considered to be “high quality”, scores of 5–8 were deemed to be “moderate quality” and studies that scored below 5 were considered to be “low quality”.[6]

RESULTS

Search results

The literature search provided a total of 173 articles identified through the combined descriptors. After examination of the titles, 93 articles were excluded for not studying recovery after exercise, not being conducted with humans, for carrying out a supplementation other than sole vitamin D or because they were systematic reviews. After the elimination of duplicates, 42 articles were selected for abstract screening and 27 of them were also excluded for not studying recovery after exercise or for being systematic reviews. Fifteen studies were then selected for full-text reading, and 5 of these were excluded for not studying recovery after exercise, not having a control group, or for reporting results inadequately. One study was added from the reference lists of selected articles, and the final number of studies in this systematic review was 11.[43,44,47-55] A summary of the search process is depicted in Figure 1.

Study characteristics

The characteristics of the included studies are summarized in Table 1. All studies were randomized controlled trials with a parallel design. One of them[48] had two experimental groups, with different baseline levels of vitamin D, and two control groups, and the results from all of them were included. Three studies[49,51,53] used more than 2 experimental arms, but only the vitamin D and control group results were reported in the review.

The sample size was 10–22 participants in each group. Only three studies[51,52,54] performed an a priori statistical power analysis and used adequate sample sizes based on those estimations. All the selected studies were conducted with healthy or apparently healthy subjects, except one[51] whose participants were considered healthy but suffered from non-specific perceived myalgia. Seven studies were conducted with men, [43,47,48,50,52,53,55] 3 with women[47,51,54] and one with men and women.[44] The mean age of the participants ranged from 15.90 ± 0.29 years to 42.40 ± 7.59 years. Five studies evaluated the effects of vitamin D supplementation on sedentary to moderately active people,[47-49,53,55] 5 studies on highly active people,[43,44,50,52,54] and one did not mention the participants fitness level.[51]

All but one study[52] evaluated the effects of regular vitamin D ingestion for a minimum period of 7 days, with a vitamin D dose per day of 600–7000 IU. Mieszkowski et al.[52] supplemented with a single dose of 150000 IU 24 h before exercise. The precise vitamin D content of the dosages and the duration of the

supplementation period are shown in Table 1. Seven studies used a special protocol to induce muscle damage,[43,47-50,52,55] which differed substantially across them (Table 1). Four studies measured functional measures, markers of muscle damage, inflammation and oxidative stress before and after a period of normal training.[44,51,53,54]

Functional measures and muscle soreness

Three studies[43,47,51] analyzed the effects of vitamin D supplementation on any of the following functional variables: maximal isometric voluntary contraction (MIVC) of the lower limb, single-leg peak power output, maximal power during a vertical jump, leg-back 'deadlift' strength, and Cooper 12-minute walk test. Only Barker et al.[47] observed a better recovery of MIVC of the lower limb in the GE. Four studies[43,47,49,51] evaluated muscle soreness after exercise, and two of them[49,51] found significantly lower values in the GE at some point after exercise or throughout the entire recovery period (Table 2).

Muscle damage

Seven studies[43,47-50,54,55] analyzed serum or plasma concentration of any of the following markers of muscle damage: aspartate aminotransferase (AST); alanine aminotransferase (ALT); myoglobin (MB); lactate dehydrogenase (LDH); creatine kinase (CK); alkaline phosphatase (ALP). All but Shanely et al.[43] observed significant differences between groups in any of the markers measured after exercise or at some point of the recovery period (Table 2).

Inflammation and oxidative stress

Six studies[44,48-50,52,53] measured any of the following inflammatory markers: tumour necrosis factor alpha (TNF-α); interleukin (IL) 1β, 6, 8, 10 and 15; C-reactive protein (CRP); antimicrobial peptide LL-37 (LL-37); follistatin-like 1 (FSTL-1); leukaemia inhibitory factor (LIF); oncostatin M (OSM); tissue inhibitor of metalloproteinase 1 (TIMP-1). All of these studies, except Todd et al.,[44] found significantly lower levels of inflammation in GE after exercise or at some point in the recovery period.

One study[53] measured serum levels of malondialdehyde (MDA), and another one[55] determined serum levels of gamma-glutamyl transferase (GGT). Both of them observed lower levels in GE at any point after exercise. A complete summary of the findings for markers of inflammation and oxidative stress can be seen in Table 2.

Methodological quality assessment

All studies were considered to be of moderate quality. Quality scores ranged from six to eight (of a maximum of 10) and had a mean PEDro score of 7.63 ± 0.67. No study

was excluded due to its low quality. Table 3 details the results of the criteria evaluated. All studies failed to blind all assessors who measured at least one key outcome (item 7) and only one three[51,53,55] carried out a concealed allocation (item 3).

DISCUSSION

Supplementation with antioxidant and anti-inflammatory substances is currently used to a substantial degree in sport to attenuate EIMD and accelerate recovery after exercise.[14,56] Vitamin D has demonstrated marked anti-inflammatory properties, and recent studies have investigated whether vitamin D supplementation attenuates muscle damage and enhances recovery after exercise. However, the results are inconclusive.

To the best of our knowledge, this is the first systematic review to examine the effectiveness of vitamin D supplementation on recovery after EIMD in humans. Eleven studies met our inclusion criteria, involving a total of 364 participants. Our review suggests that vitamin D supplementation may attenuate the extent of muscle damage and inflammation, subsequently enhancing recovery after exercise.

Functional measures and muscle soreness

Of the three studies that evaluated muscle function,[43,47,51] only Barker et al.[47] observed a better recovery of the MVIC of the lower limb in the GE 24 h after exercise. Abdeen et al.[51] also noticed an increase in the distance covered during the Cooper test, but this increase was not significant. Of the four studies that measured muscle soreness, Barker et al.[47] and Shanely et al.[43] did not find significantly lower muscle soreness values in GE, that vitamin D supplementation attenuated muscle soreness, although Barker et al.[47] observed a tendency. However, the other two articles[49,51] obtained lower levels of muscle soreness in the GE, suggesting that vitamin D supplementation does, in fact, reduce muscle soreness.

Only Shanely et al.[43] did not observe a better recovery of muscle function or a reduction in muscle soreness and not even a tendency. They used a dosage of 600 IU/day, a particularly low amount of vitamin D compared to the other studies, potentially explaining why they did not achieve the expected results. Moreover, the authors did not even find differences between groups in serum vitamin D levels after a supplementation period of 7 weeks.

It appears that vitamin D supplementation with 4000 IU/day or more for more than 7 days could, therefore, accelerate the recovery of functional measures and attenuate muscle soreness after EIMD. However, due to the few studies included and

because not all of them obtained positive results, new studies are required to confirm the effectiveness of vitamin D supplementation.

Muscle damage

Six of the seven studies that analyzed muscle damage obtained significantly lower values in the GE in any of the markers measured after exercise or at some point during the recovery period. Only Shanely et al.[43] did not observe significant differences between groups. Again, the low daily dosages of vitamin D may be the cause of these unexpected results. Recently, Iolascon et al.[57] investigated the effects of vitamin D on muscle tissue through genomic and non-genomic pathways, concluding that vitamin D supplementation enhances the structural and functional restoration of the muscles, by increasing the expression of myogenic factors in satellite cells during recovery from muscle damage.

In this sense, our review indicates that supplementation with dosages of 2000 IU/day or more for a total period of more than 7 days is an effective strategy for reducing EIMD. Supplementations with other functional foods, such as tart cherry or pomegranate,[13,14] have obtained contradictory results, with some studies reporting beneficial effects and others not. Thus, we can conclude that vitamin D supplementation seems to be more effective for attenuating EIMD.

Inflammation

Six of the seven studies that analyzed inflammatory markers,[44,48-50,52,53] found significantly lower values in the GE. The reason why Todd et al.[44] did not observe those results may have been that they did not study inflammation after a particular protocol to induce muscle damage, but after normal training sessions. Those normal sessions might not have generated sufficient muscle damage and, therefore, vitamin D supplementation conferred no benefits for inflammation. In addition, biochemical analyses were not performed after the training but the next morning, after an overnight fast, and the biomarkers would have already reached their normal ranges in both groups. In fact, the concentrations of most of the cytokines that the authors wished to analyze were undetectable or fell below the lower limit of detection and were finally excluded from the statistical analyses.[44]

There is some controversy regarding whether vitamin D reduces inflammation or, on the contrary, it is inflammation that reduces vitamin D levels.[28,58] However, there is some evidence that has associated various inflammatory diseases and vitamin D deficiency and that has outlined the potential role of vitamin D supplementation for

reducing the risk of developing those diseases.[28] Regarding the exercise-induced inflammation, our results suggest that vitamin D supplementation for more than a week with dosages of more than 2000 IU/day lowers the inflammatory response triggered after EIMD.

After analyzing the results of other systematic reviews on supplementations with tart cherry, pomegranate or beetroots,[14,15] with some studies not reporting beneficial effects on inflammation levels, we can conclude that vitamin D supplementation seems to be more effective for reducing inflammation after exercise than other functional foods.

Oxidative stress

The positive effects on lowering oxidative stress markers observed by Vakili et al.[49] and Mastali et al.[55] indicate that vitamin D might have antioxidant properties. However, these findings may have been due to reduced inflammation because, after muscle damage is generated, the inflammatory response further increases ROS production.[59] Therefore, if vitamin D reduces inflammation, it could also have reduced oxidative stress indirectly.

According to Mokhtari et al.,[60] it seems that vitamin D plays an important role in the prevention of some chronic diseases, such as diabetes, because it regulates oxidative stress. However, the authors conclude that there are few 'in vivo' studies that have examined that hypothesis. More recently, Tagliaferri et al.,[61] in their review of randomized controlled trials conducted with humans, concluded that the role of vitamin D as an antioxidant cannot be confirmed because contradictory results have been provided in the literature to date. Our findings suggest that vitamin D reduces oxidative stress after exercise, but there were only two studies included. Therefore, new scientific evidence is required to confirm the antioxidant effect of vitamin D supplementation.

Limitations

This review has several limitations: 1) Not all the studies used a specific protocol to induce muscle damage and when they did, the exercise protocol varied substantially between them, inducing different levels of muscle damage. Moreover, the varying training statuses of the participants affected the magnitude of the muscle damage experienced. 2) Only three studies performed an a priori statistical power analysis; therefore, the sample sizes may not have been sufficiently large to detect small

changes in the markers analyzed. 3) There were substantial differences in the dosages of vitamin D and in the supplementation periods.

CONCLUSIONS

Despite the limitations mentioned, the studies included in this systematic review suggest that vitamin D supplementation, with at least 2000 IU/day, during periods of one week or more, reduces muscular damage and inflammation after exercise. Studies regarding the effects on muscular function and muscle soreness are scarce and they show contradictory results; further research is warranted. Only two studies investigated the effects of vitamin D supplementation on oxidative stress and despite the positive results observed, further analyses are also necessary. These new investigations should focus on determining the optimal vitamin D dosage to obtain positive effects and the possible adverse effects of supplementation for periods of more than three months.

Author contributions

The study was designed by the two authors. Conceptualization, investigation, methodology, study selection, data extraction, data interpretation, writing, editing, and preparation of the manuscript were also undertaken by the two authors. Both authors reviewed and approved the final version of the article.

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Conflicts of interest

The authors declare no conflicts of interest.

REFERENCES

1. Phaniendra A, Jestadi DB, Periyasamy L. Free radicals: properties, sources, targets, and their implication in various diseases. Indian J Clin Biochem. 2015;30:11–26.
2. Pham-Huy LA, He H, Pham-Huy C. Free radicals, antioxidants in disease and health. Int J Biomed Sci. 2008;4:89–96.
3. Valko M, Leibfritz D, Moncol J, Cronin MT, Mazur M, Telser J. Free radicals and antioxidants in normal physiological functions and human disease. Int J Biochem Cell Biol. 2007;39:44–84.
4. Di Meo S, Reed TT, Venditti P, Victor VM. Role of ROS and RNS sources in physiological and pathological conditions. Oxid Med Cell Longev. 2016; 1245049.

5. Bloomer RJ, Goldfarb AH. Anaerobic exercise and oxidative stress: a review. Can J Appl Physiol. 2004;29:245–63.
6. Howatson G, van Someren KA. The prevention and treatment of exercise-induced muscle damage. Sports Med. 2008:38:483–503.
7. Jackson MJ, Vasilaki A, McArdle A. Cellular mechanisms underlying oxidative stress in human exercise. Free Radic Biol Med. 2016;98:13–7.
8. Reid MB. Redox modulation of skeletal muscle contraction: what we know and what we don't. J Appl Physiol. 2001;90:724–731.
9. Powers SK, Ji LL, Kavazis AN, Jackson MJ. Reactive oxygen species: impact on skeletal muscle. Compr Physiol. 2011;1:941–969.
10. O'Fallon K, Kaushik D, Michniak-Kohn B, Dunne CP, Zambraski EJ, Clarkson PM. Effects of Quercetin Supplementation on Markers of Muscle Damage and Inflammation After Eccentric Exercise. Int J Sport Nutr Exerc Metab. 2012;22(6):430–437.
11. Donnelly AE, McCormick K, Maughan RJ, Whiting PH, Clarkson PM. Effects of a non-steroidal anti-inflammatory drug on delayed onset muscle soreness and indices of damage. Br J Sports Med. 1988;22:35–38.
12. Fraga CG, Croft KD, Kennedy DO, Tomás-Barberán FA. The effects of polyphenols and other bioactives on human health. Food Func. 2019;10:514–528.
13. Ammar A, Bailey SJ, Chtourou H, Trabelsi K, Turki M, Hökelmann A, et al. Effects of pomegranate supplementation on exercise performance and post-exercise recovery in healthy adults: a systematic review. Br J Nutr. 2018;120(11):1201–1216.
14. Rojano D, Molina A, Moya H, Berral FJ. Tart cherry and pomegranate supplementations enhance recovery from exercise-induced muscle damage: a systematic review. Biol Sport. 2021;38(1):97–111.
15. Rojano-Ortega D. Regular, but not acute, green tea supplementation increases total antioxidant status and reduces exercise-induced oxidative stress: a systematic review. Nutr Res. 2021;94: 34–43.
16. Cannell JJ, Hollis BW, Sorenson MB, Taft TN, Anderson JJ. Athletic performance and vitamin D. Med Sci Sports Exerc. 2009;41:1102–1110.
17. Bover J, Egido J, Fernández-Giráldez E, Praga M, Solozábal-Campos C, Torregrosa TV, et al. Vitamina D, receptor de la vitamina D e importancia de su

activación en el paciente con enfermedad renal crónica. Nefrologia. 2015;35(1):28–41.

18. Holick MF. Vitamin D deficiency. N Engl J Med. 2007;357(3):266–281.
19. EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA), Scientific Opinion on the substantiation of health claims related to vitamin D and maintenance of bone and teeth (ID 150, 151, 158), absorption and utilization of calcium and phosphorus and maintenance of normal blood calcium concentrations (ID 152, 157), cell division (ID 153), and thyroid function (ID 156) pursuant to Article 13(1) of Regulation (EC) No 1924/2006. EFSA J. 2009;7(9):1227.
20. Larson-Meyer E. La importancia de la vitamina D en los atletas. Sports Sci Ex. 2015;28(148):1–6.
21. EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA). Scientific Opinion on the substantiation of health claims related to vitamin D and normal function of the immune system and inflammatory response (ID 154, 159), maintenance of normal muscle function (ID 155) and maintenance of normal cardiovascular function (ID 159) pursuant to Article 13(1) of Regulation (EC) No 1924/2006. EFSA J. 2010;8(2):1468.
22. Guo XF, Wang C, Yang T, Li S, Li KL, Li D. Vitamin D and non-alcoholic fatty liver disease: a meta-analysis of randomized controlled trials. Food Func. 2020;11(9):7389–7399.
23. Olick MF. Sunlight and vitamin D for bone health and prevention of autoimmune disease, cancers and cardiovascular disease. Am J Clin Nutr. 2004;80(S1):1678S–1688S.
24. Vaughan M, Trott M, Sapkota R, Premi G, Roberts J, Ubhi J, et al. Changes in 25-hydroxyvitamin D levels post-vitamin D supplementation in people of Black and Asian ethnicities and its implications during COVID-19 pandemic: A systematic review. J Hum Nutr Diet. 2021:1–11.
25. Chiang M, Ismaeel A, Griffis RB, Weems S. Effects of vitamin D supplementation on muscle strength in athletes: a systematic review. J Strength Cond Res. 2017;31(2):566–574.
26. He S, Aw Yong XH, Walsh NP, Gleeson M. Is there an optimal vitamin D status for immunity in athletes and military personnel? Exerc Immunol Rev. 2016;22(63):42–64.

27. Shuler D, Wingate MK, Moore GH, Giangarra C. Sports health benefits of vitamin D. Sports Health. 2012;4(6):496–501.
28. Yin K, Agrawal DK. Vitamin D and inflammatory diseases. J Inflamm Res. 2014;7:69–87.
29. Chagas E, Borges MC, Martini LA, Rogero MM. Focus on vitamin D, inflammation and type 2 diabete. Nutrients. 2012;4(1):52–67.
30. Choi M, Park H, Cho S, Lee M. Vitamin D3 supplementation modulates inflammatory responses from the muscle damage induced by high-intensity exercise in SD rats. Cytokine. 2013;63:27–35.
31. Liu J. Vitamin D content of food and its contribution to vitamin D status: a brief overview and Australian focus. Photochem Photobiol Sci. 2012;11(12):1802–1807.
32. Pilz S, Kienreich K, Rutters F, de Jongh R, van Ballegooijen AJ, Grubler M, et al. Role of vitamin D in the development of insulin resistance and type 2 diabetes. Curr Diab Rep. 2013;13(2):261–270.
33. Querfeld U. Vitamin D and inflammation. Pediatr Nephrol. 2013;28:605–610.
34. Hollis BW, Wagner CL, Drezner MK, Binkley NC. Circulating vitamin D3 and 25-hydroxyvitamin D in humans: An important tool to define adequate nutritional vitamin D status. J Steroid Biochem Mol Biol. 2007;103:631–634.
35. Raimundo V, Faulhaber CA, Menegatti PK, Marques Lda S, Furlanetto TW. Effect of high- versus low-fat meal on serum 25-hydroxyvitamin D levels after a single oral dose of vitamin D: A single-blind, parallel, randomized trial. Int J Endocrinol. 2011:809069.
36. Ross AC, Manson JE, Abrams SA, Aloia JF, Brannon PM, Clinton SK, et al. The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: What clinicians need to know. J Clin Endocrinol Metab. 2011;96:53–58.
37. Varsavsky M, Rozas Moreno P, Becerra Fernández A, Luque Fernández I, Quesada Gómez JM, Ávila Rubio V, et al. Recomendaciones de vitamina D para la población general. Endocrinol Diab Nutr. 2017;64(S1):7–14.
38. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2011;96(7):1911–1930.

39. Adebayo A, Itkonen ST, Öhman T, Kiely M, Cashman KD, Lamberg-Allardt C. Safety of Vitamin D Food Fortification and Supplementation: Evidence from Randomized Controlled Trials and Observational Studies. Foods, 2021;10:3065.
40. Gunton JE, Girgis CM. Vitamin D and muscle. Bone Rep. 2018;8:163–167.
41. Barker T, Martins TB, Hill HR, Kjeldsberg CR, Dixon BM, Schneider ED, et al.Vitamin D sufficiency associates with an increase in anti-inflammatory cytokines after intense exercise in humans. Cytokine. 2014;65(2):134–137.
42. Sun X, Cao ZB, Zhang Y, Ishimi Y, Tabata I, Higuchi M. Association between serum 25- Hydroxyvitamin D and inflammatory cytokines in healthy adults. Nutrients. 2014;6(1):221–230.
43. Shanely RA, Nieman DC, Knab AM, Gillitt ND, Meaney MP, Jin F, et al. Influence of vitamin D mushroom powder supplementation on exercise-induced muscle damage in vitamin D insufficient high school athletes. J Sports Sci. 2014;32(7):670–679.
44. Todd JJ, McSorley EM, Pourshahidi LK, Madigan SM, Crowe W, Laird EJ, et al. Oral spray wintertime vitamin D3 supplementation has no impact on inflammation in Gaelic footballers. Scand J Med Sci Sports. 2017;27(11):1300–1307.
45. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. Ann Intern Med. 2009;151(4):65–94.
46. Verhagen P, de Vet HC, de Bie RA, Kessels AG, Boers M, Bouter LM, et al. The Delphi list: a criteria list for quality assessment of randomized clinical trials for conducting systematic reviews developed by Delphi consensus. J Clin Epidemiol. 1998;51:1235–1241.
47. Barker T, Schneider ED, Dixon BM, Henriksen VT, Weaver LK. Supplemental vitamin D enhances the recovery in peak isometric force shortly after intense exercise. Nutr Metab. 2013;10(1):69.
48. Pilch W, Kita B, Piotrowska A, Tota Ł, Maciejczyk M, Czerwińska-Ledwig O, et al. The effect of vitamin D supplementation on the muscle damage after eccentric exercise in young men: a randomized, control trial. J Int Soc Sports Nutr. 2020;17:53.

49. Vakili S, Ghasemi F, Rahmati-Ahmadabad S, Amini H, Iraji R, Seifbarghi T, et al. Effects of Vibration therapy and vitamin D Supplement on eccentric exercise-induced delayed onset musde soreness in female students. Comp Exerc Physiol. 2020;16(4):267–275.
50. Żebrowska A, Sadowska-Krępa E, Stanula A, Waśkiewicz Z, Łakomy O, Bezuglov E, et al. The effect of vitamin D supplementation on serum total 25(OH) levels and biochemical markers of skeletal muscles in runners. J Int Soc Sports Nutr. 2020;17:18.
51. Abdeen AA, Rodriguez-Sanz D, Ewidea M, Al-Hamaky DMA, Mohamed MAE, Elerian AE. Efficacy of Vitamin D Supplementation in Addition to Aerobic Exercise Training in ObeseWomen with Perceived Myalgia: A Single-Blinded Randomized Controlled Clinical Trial. Nutrients. 2021;13(6):1819.
52. Mieszkowski J, Borkowska A, Stankiewicz B, Kochanowicz A, Niespodzinski B, Surmiak M, et al. Single High-Dose Vitamin D Supplementation as an Approach for Reducing Ultramarathon-Induced Inflammation: A Double-Blind Randomized Controlled Trial. Nutrients. 2021;13(4):1280.
53. Nikniaz L, Ghojazadeh M, Nateghian H, Nikniaz Z, Farhangi MA, Pourmanaf H. The interaction effect of aerobic exercise and vitamin D supplementation on inflammatory factors, anti-inflammatory proteins, and lung function in male smokers: a randomized controlled trial. BMC Sports Sci Med Rehabil. 2021;13:102.
54. Stojanović E, Jakovljević V, Scanlan AT, Dalbo VJ, Radovanović D. Vitamin D3 supplementation reduces serum markers of bone resorption and muscle damage in female basketball players with vitamin D inadequacy. Eur J Sport Sci. 2021;25:1–11.
55. Mastali VP, Hoseini R, Azizi M. The short-term effect of vitamin D supplementation on the response to muscle and liver damages indices by exhaustive aerobic exercise in untrained men: a quasi-experimental study. BMC Sports Sci Med Rehabil. 2022;14:7.
56. Peake JM, Suzuki K, Coombes JS. The influence of antioxidant supplementation on markers of inflammation and the relationship to oxidative stress after exercise. J Nutr Biochem. 2007;18(6):357–371.
57. Iolascon G, Moretti A, Paoletta M, Liguori S, Di Munno O. Muscle Regeneration and Function in Sports: A Focus on Vitamin D. Medicina. 2021;57:1015.

58. Cannell J, Grant WB, Holick MF. Vitamin D and inflammation. Derm-Endocrinol. 2014;6(1):e983401.
59. Chazaud B. Inflammation during skeletal muscle regeneration and tissue remodeling: Application to exercise-induced muscle damage management. Immunol Cell Biol. 2016;94(2):140–145.
60. Mokhtari Z, Hekmatdoost A, Nourian M. Antioxidant efficacy of vitamin D. J Parathyr Dis. 2017;5(1):11–16.
61. Tagliaferri S, Porri P, De Giuseppe R, Manuelli M, Alessio F, Cena H. The controversial role of vitamin D as an antioxidant: results from randomized controlled trials. Nutr Res Rev. 2019;32:99–105.

Tables

Table 1. Characteristics of the included studies.

Study	Participants	Groups	Age (years)	Vitamin D content	Supplementation period	Exercise protocol to induce muscle damage
Barker et al. (2013)	Healthy and modestly active men	15 (VITD) 13 (CON)	30 ± 6 31 ± 5	4000 IU/day	35 days (exercise on day 28)	10 sets of 10 repetitive jumps at 75% of body mass with 20 s rest between sets
Shanely et al. (2014)	Male healthy students participating in varsity sports	17 (VITD) 16 (CON)	16.6 ± 0.23 15.9 ± 0.29	600 IU/day	42 days (exercise on day 42)	Modified Lough-borough Intermittent Shuttle Test + leg lunges
Todd et al. (2017)	Healthy male and female young gaelic footballers	22 (VITD) 20 (CON)	20 ± 2 20 ± 2	3000 IU/day	12 weeks	Normal training
Pilch et al. (2020)	Healthy young men with low or moderate physical activity	18 (VITD1) 18 (CON1) 18 (VITD2) 18 (CON2)	20-24	Specific for each athlete (more than 2000 IU/day)	3 months (exercise at the end)	Incremental exercise test to voluntary exhaustion on a treadmill
Vakili et al. (2020)	Healthy young untrained female students	15 (VITD) 15 (CON)	24.73 ± 1.57 24.53 ± 1.59	3800 IU/day	7 días (exercise on day 7)	5 sets of 4 repetitions of quadriceps leg extension at 120% de 1RM with both legs
Żebrowska et al. (2020)	Male ultramarathon caucasian runners	12 (VITD) 12 (CON)	33.7 ± 7.5 35.9 ± 5.3	2000 IU/day	21 days (exercise at the end)	30-min downhill running test at 70% of the individual VO2peak
Abdeen et al. (2021)	Relatively healthy obese women	15 (VITD) 15 (CON)	34.8 ± 2.64 35.4 ± 2.69	50000 IU/week (~ 7000 IU/day)	12 weeks	Normal training

Mieszkowski et al. (2021)	Healthy male semi-professional ultramarathon runners	16 (VITD) 19 (CON)	42.40 ± 7.59 39.48 ± 6.89	150000 IU	One single dose (24 h before exercise)	Ultramarathon
Nikniaz et al. (2021)	Healthy sedentary male smokers	10 (VITD) 10 (CON)	30.40 ± 4.08 31.30 ± 4.00	6000 IU/week (1000/day except fridays	28 days	Normal training
Stojanović et al. (2021)	Healthy female professional or semi-professional young basketball players	12 (VITD) 12 (CON)	19.4 ± 4.0 19.8 ± 4.6	4000 IU/day	42 days	Normal training
Mastali et al. (2022)	Healthy non-athlete men	13 (VITD) 13 (CON)	24.33 ± 2.7 25.83 ± 3.18	2000 IU/day	42 days (exercise at the end)	Exhaustive Bruce aerobic test

VITD: vitamin D group; CON: control group; COD: cross-over design; IU: international units; RM: repetition maximum.

Table 2. Variables measured and summary of findings of the included studies.

Estudio	Functional measures and muscle soreness	Biochemical markers of muscle damage, inflammation and oxidative stress	Significant differences in VITD group (vs CON group).
Barker et al. (2013)	Muscle soreness of the lower limb, MIVC and peak power of the lower limb Measurements: baseline, pre, post, 1 h, 24 h, 48 h, 72 h and 168 h post	Plasma: AST, ALT Measurements: baseline, pre, post and 1 h, 24 h, 48 h, 72 h and 168 h post	> Recovery of MIVC 24 h post < AST 168 h post < ALT 48 h and 72 h post
Shanely et al. (2014)	Muscle soreness, vertical jump power and leg-back "dead.lift" strength Measurements: baseline, pre, post, 24 h and 48 h post	Serum: MB, LDH, CK, AST Measurements: baseline, pre, post and 24 h and 48 h post	No significant differences between groups
Todd et al. (2017)	----------	Plasma: TNF-α, IL-8, CRP, LL-37. Measurements: pre and post (after an overnight fast)	No significant differences between groups
Pilch et al. (2020)	---------	Serum: MB; Plasma: CK y LDH; Serum: IL-1β Measurements: pre, 1 h post and 24 h post	< CK pre and 1 h post (group 2) < LDH pre and 1 h post (group 1) < IL-1β pre and 1 h post (group 1)
Vakili et al. (2020)	Muscle soreness Measurements: baseline, pre, 24 h, 48 h and 72 h post	Serum: CK; Serum: IL-6; Serum: MDA Measurements: baseline, pre, 24 h, 48 h and 72 h post	< muscle soreness 24 and 48 h post < CK 48 h post < IL-6 24 h and 48 h post < MDA 48 h and 72 h post (comparisons between groups not reported but great differences observed)
Żebrowska et	----------	Serum: MB, CK, LDH	< CK 24 h post

al. (2020)		Serum: IL-6; TNF-α Measurements: baseline, pre, post, 1 h and 24 h post	< IL-6 24 h post
Abdeen et al. (2021)	Cooper 12-minute walk test, muscle soreness Measurements: baseline and post (after an overnight fast)	---------	< muscle soreness post
Mieszkowski et al. (2021)	----------	Serum: FSTL-1, IL-6, IL-10, IL-15, resistin, LIF, OSM, TIMP-1 Measurements: 24 h pre, post and 24 h post	< IL-6; IL-10 and resistin post
Nikniaz et al. (2021)	----------	Serum: IL-6, TNF-α Measurements: baseline and 24 h post (after an overnight fast)	< TNF-α post < IL-6 post (tendency)
Stojanović et al. (2021)	----------	Serum: LDH, CK. Measurements: baseline and 36 h post (after an overnight fast)	< LDH variation post < CK variation post
Mastali et al. (2022)	----------	Serum: CK, LDH, ALT, AST, ALP; Serum: GGT Measurements: pre and post	< LDH and CK post < ALT, AST, GGT and ALP pre and post

MIVC: maximal isometric voluntary contraction; AST: aspartate transaminase; ALT: alanine aminotransferase; MB: myoglobin; LDH: lactate dehydrogenase; CK: creatine kinase; TNF-α: tumor necrosis factor alpha; IL: interleukin; CRP: C-reactive protein; LL-37: antimicrobial peptide LL-37; MDA: malondyaldehyde; FSTL-1: follistatin-like 1; LIF: leukaemia inhibitory factor; OSM: oncostatin M; TIMP-1: tissue inhibitor of metalloproteinase 1; ALP: alkaline phosphatase; GGT: gamma-glutamyl transferase.

Table 3. Methodological quality of the included studies assessed with the PEDro scale.

Items	Barker et al. (2013)	Shanely et al. (2014)	Todd et al. (2017)	Pilch et al. (2020)	Vakili et al. (2020)	Żebrowska et al. (2020)	Abdeen et al. (2021)	Mieszkowski et al. (2021)	Nikniaz et al. (2021)	Stojano-vić et al. (2021)	Mastali et al. (2022)
1. Eligibility criteria were specified	+	+	+	+	+	+	+	+	+	+	+
2. Subjects were randomly allocated to groups (in a crossover study, subjects were randomly allocated an order in which treatments were received)	+	+	+	+	+	+	+	+	+	+	+
3. Allocation was concealed	-	-	-	-	-	-	+	-	+	-	+
4. The groups were similar at baseline regarding the most important prognostic indicators	+	+	+	+	+	+	+	+	+	-	+
5. There was blinding of all subjects	+	+	+	+	+	+	+	+	-	+	+
6. There was blinding of all therapists who administered the therapy	+	+	+	-	+	+	-	+	-	+	-
7. There was blinding of all assessors who measured at least one key outcome	-	-	-	-	-	-	-	-	-	-	-
8. Measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups	+	+	-	-	+	+	+	+	+	+	+

9. All subjects for whom outcome measures were available received the treatment or control condition as allocated or, where this was not the case, data for at least one key outcome was analysed by "intention to treat"	+	+	+	+	+	+	+	+	+	+	+
10. The results of between-group statistical comparisons are reported for at least one key outcome	+	+	+	+	+	+	+	+	+	+	+
11. The study provides both point measures and measures of variability for at least one key outcome	+	+	+	+	+	+	+	+	+	+	+
Total Score	8	8	8	6	8	8	8	8	7	7	8

Figure Legends

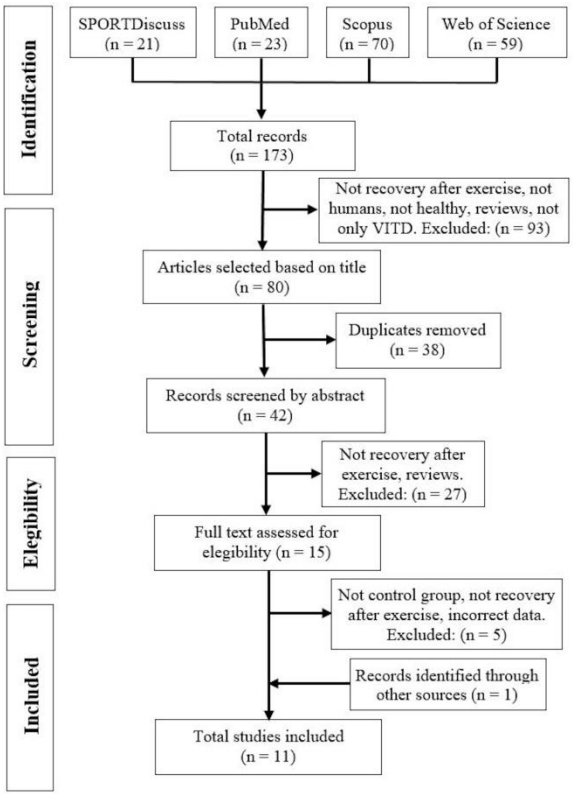

Figure 1. Flowchart for identification and selection of eligible studies for the systematic review