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SYSTEMATIC REVIEWS

Systematic review and meta-analysis on vitamin C in musculoskeletal disorders

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Abstract

BACKGROUND

Chronic pain and musculoskeletal disorders (MSDs) are prevalent and impact health around the world. Traditional treatments may not always be effective and safe.

AIM

To determine the effectiveness of vitamin C supplementation on reducing pain, improving function and supporting tissue repair in MSDs.

METHODS

Randomized controlled trials, cohort studies, and observational studies that assessed the impact of vitamin C on MSDs. The Cochrane Risk of Bias tool was used to evaluate the quality of studies. Standardized mean differences (SMD) were pooled using random-effects meta-analysis.

RESULTS

Thirty studies were included in the meta-analysis. Vitamin C significantly reduced pain (SMD = -0.68; 95% confidence interval: -0.87 to -0.49) and improved function (SMD = 0.61; 95% confidence interval: 0.45-0.77). Collagen synthesis and inflammatory markers (C-reactive protein, interleukin-6 and tumor necrotizing factor-α) were all consistently improved.

CONCLUSION

Vitamin C supplementation might have additional benefits in some MSDs, such as reducing pain and inflammatory modulation. But there is currently little consistency in the evidence and medium quality of the methods used. No definitive therapeutic efficacy can be determined, and further well-designed, disorder-specific randomized controlled trials are required.

Key Words: Vitamin C; Musculoskeletal disorders; Analgesia; Inflammation; Tissue repair; Antioxidants

Core Tip: Vitamin C is a promising additive medication for musculoskeletal disorders with its potential benefits in terms of pain reduction, functional improvement, and tissue regeneration. Its effects on collagen production and reducing inflammation has been confirmed in 30 studies. Based on these results, vitamin C can be added to the treatment protocol of musculoskeletal disorders and the findings stress the need for further well-designed and tightly controlled trials to define the optimal doses and clarify the therapeutic role of vitamin C in orthopaedic medicine.

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INTRODUCTION

Musculoskeletal disorders (MSDs) refer to a group of disorders affecting the muscles, bones, joints, ligaments and tendons, which may cause pain, discomfort and disability. They include things such as rheumatoid arthritis, osteoarthritis, osteoporosis and tendinitis, which can make a person's mobility and quality of life significantly restricted. MSDs significantly affect the world, as millions of people suffer from chronic pain, physical functioning impairments and shortened lifespan. The occurrence of such disorders is rising with the ageing of populations, and these disorders are linked with sedentary lifestyle and poor nutrition habits, which are known risk factors for MSD in developed countries, particularly[1,2]. The cost to health care systems is equally huge globally. Recent studies indicate that MSDs account for a large proportion of health care costs, mostly due to the long-term care, rehab, and loss of productivity. There can be high indirect costs of medical care, including loss of work and reduction in work productivity of affected people. With the ageing of the general population, the need for effective treatment and interventions for these disorders is growing in urgency.

The use of vitamin C (ascorbic acid) is one of the areas that is promising in the management of MSDs; vitamin C is an essential water-soluble vitamin whose major role is in the synthesis of collagen. Collagen is a structural protein that gives support and strength to the connective tissues including tendons, ligaments and cartilage. Collagen is essential for a healthy musculoskeletal (MSK) system and a key component in the ability to heal and regenerate tissues after injuries or inflammation, making vitamin C important for MSK health[3,4].

Vitamin C is a strong antioxidant that reduces oxidative stress, which is linked to MSD[5,6]. Moreover, vitamin C has been found to be effective in the condition of bone health. It stimulates the growth of osteoblasts (cells that create the bone) and may help prevent bones from losing mass due to osteoporosis or heal fractures. In the above-discussed

multifaceted role of vitamin C in MSK health, there is a growing interest in the therapeutic use of vitamin C supplementation in MSDs, as a complementary therapy or as a single therapy in some instances.

The use of vitamin C in the treatment of MSDs has shown a promising potential; however, the available literature has so far been limited and is not consistent in terms of study design, sample size, and outcome measures. There are some studies that indicate that there are benefits in terms of pain relief, reduction in inflammation and functional improvement, and some that report mixed and/or inconclusive. The results of this review have been inconsistent, necessitating a systematic review and meta-analysis of the available evidence to provide more focused conclusions and guide clinical practice.

A full systematic review is beneficial to assess which specific MSDs are most likely to benefit from vitamin C supplementation and the best dose. In addition, it can provide information on whether vitamin C is part of a comprehensive treatment or if it is an effective treatment on its own. Some existing studies have investigated the effect of vitamin C in particular MSDs, such as osteoarthritis, rheumatoid arthritis and tendinitis, but there is no strong consensus regarding the effect of vitamin C on different disease pathways and if it is safe and effective to use vitamin C as part of routine care[7,8].

Although MSDs are a heterogeneous collection of disorders of varied etiologies, there are commonalities in the way that they generate symptoms and tissue breakdown across multiple types of MSDs[9,10], including oxidative stress, activation of inflammatory signaling, and collagen synthesis impairment. This vitamin C works at these convergent biological interfaces rather than targeting specific mechanisms of disease. Thus, it may exert different effects, depending on the disorder, and interpretation must be done disorder-specifically. This review is a summary of evidence from all the MSD categories and includes subgroup analyses to take into account pathophysiological heterogeneity.

MATERIALS AND METHODS

There are several bits and pieces of evidence regarding the use of vitamin C in MSDs. Various trials indicate pain-relieving and healing properties, but there is no agreement on dosage or whether certain diseases are more responsive to treatment. International Prospective Register of Systematic Reviews registration No. CRD420251065484.

Research questions

The main research questions for this systematic review and the meta-analysis are listed below: (1) What is the effectiveness of vitamin C supplementation to decrease pain, function and recovery in people with MSDs? And (2) Which are the best doses of vitamin C to use when treating various types of MSK conditions?

PICO (Population, Intervention Comparison, Outcomes) framework

Population: Adults who have MSDs.

Intervention: Oral vitamin C supplementation (500-2000 mg/day).

Comparator: Placebo or standard treatment (non-steroidal anti-inflammatory drugs, glucosamine, *etc.*).

Outcomes: Pain reduction, functional improvement, tissue repair.

Inclusion criteria

We aimed to accept a wide range of study designs in this systematic review and meta-analysis to examine the effects of vitamin C supplementation on MSDs from as wide a spectrum as possible of study designs. Studies are randomized controlled trials, cohort studies, observational studies and systematic reviews. We call these types of studies the gold standard studies in clinical research because they can offer us both controlled data (randomized controlled trials) and real-world data (cohort and observational studies). The analysis is designed to provide a comprehensive overview of the effects of vitamin C on MSDs by incorporating a variety of study designs[11,12].

The studies specifically should have examined the impact of vitamin C supplements on outcomes, including pain, inflammation and tissue repair, of people with a diagnosis of MSDs. Reducing pain is an important effect because it helps to improve the quality of life of a patient, and reducing inflammation and repairing tissues is important in the treatment of diseases such as osteoarthritis, tendinitis and rheumatoid arthritis. To ensure that only relevant data were analyzed, studies were only included in the analyses of the meta-analysis if they measured one or more of these outcomes. These outcomes specifically guided the review, and a comprehensive evaluation of the effectiveness of vitamin C supplementation for the management and prevention of MSD symptoms was sought[13].

Search strategy and data sources

An extensive literature search was performed, following PRISMA 2020. The following electronic databases were systematically searched: PubMed, MEDLINE, Scopus, EMBASE, Web of Science, Cochrane Library and Google Scholar. The search period was from January 2000 to November 2024 to include recent evidence regarding vitamin C supplementation in MSDs[13,14].

The search strategy used controlled vocabulary terms in combination with free text terms: "vitamin C" OR "ascorbic acid" AND "musculoskeletal disorders" OR "MSDs" OR "osteoarthritis" OR "fracture" OR "tendinopathy" OR "complex regional pain syndrome" AND "pain" OR "function" OR "inflammation" OR "collagen synthesis". Boolean operators (AND/OR) were used to narrow down the results. Data were not extracted directly from reviews to prevent double-

counting; however, reference lists of relevant systematic reviews were screened to identify additional eligible studies to search[15].

We have the data extracted and quality assessed. The data has been extracted and checked for quality. After the selection of studies, data extraction was carried out in detail to collect relevant data for every study. The extraction process included determining relevant aspects, including the study design, number of participants, dosage of the intervention, outcome measured, and the length of the study. This detailed extraction allowed for clarity about the contribution each study made to the meta-analysis and for accurate comparison of studies. Each study used a specific dosage of vitamin C, and if the dosage changed, this could affect the results and conclusions drawn from the study, whether vitamin C is effective or not in treating MSDs[16,17].

Furthermore, there was an appraisal of the methodological quality of the individual studies in the review. A critical evaluation of the design of the study, risk of bias, and overall quality of the study was performed to ensure that only high-quality studies were included in the final analysis. The method included the widely accepted and established Cochrane Risk of Bias tool that evaluates the risk of bias of randomized trials on various dimensions, including selection bias, performance bias, detection bias and attrition bias[18,19]. These highly effective tools of quality assessment were used to ensure that all studies used in the meta-analysis were scientifically sound. The PRISMA flow diagram is summarized in Figure 1 and the summary of included studies in Table 1.

Statistical analysis

The main data analysis consisted of a synthesis of the data obtained from the different studies, which was carried out with statistical methods widely used in a meta-analysis, to obtain a pooled estimate of the treatment effects. The standardized mean difference (SMD) was one of the most widely used metrics for comparisons of the effect size across studies that report on different outcome measures[20,21]. The meta-analysis was able to pool data from studies that used different assessment scales or tools but were measuring similar outcomes, such as pain relief or functional improvement, because it calculated the SMD.

To visualize the effects of vitamin C supplementation on MSDs, forest plots were created. Forest plots are descriptive graphs that display individual study effect sizes and the summarizing (pooled) effect size, which gives a clear overview of the variability in the results among the studies. These plots also reflect heterogeneity, that is, the variation of the results of the studies from one to another. Increased heterogeneity might be a sign that the effect of vitamin C differs considerably between the different MSD and/or treatment conditions, and decreased homogeneity might represent a more homogeneous effect[22].

Lastly, funnel plots were used to assess publication bias. Meta-analyses often use funnel plots to visually assess for bias in the studies included, especially if studies with significant results are more likely to be published than studies with null or negative results. Publication bias can affect the overall conclusions of the meta-analysis, and this analysis helped minimize the effects of publication bias[23]. RevMan 5.4 was used for conducting meta-analyses. The I^2 statistic and the χ^2 test were used to assess heterogeneity ($P < 0.10$ was considered significant). The Egger's regression test was used to assess the publication bias.

The level of statistical heterogeneity was measured by the proportion I^2 and the Tau^2 value, where I^2 values of < 25%, 25%-50% and > 50% indicated low, moderate and high heterogeneity, respectively. A random-effects model was chosen a priori because of clinical and methodological variation assumed. Studies with a high risk of bias were omitted in sensitivity analyses, and analyses were done by MSD subtype. Inverse variance methods were used to calculate study weights.

RESULTS

The study selection for this systematic review and meta-analysis was carried out through extensive literature screening. The search of several databases (PubMed, MEDLINE, Scopus, EMBASE and Google Scholar) resulted in the identification of 200 studies at first. Following the screening process of checking relevance, 45 studies were identified as relevant for detailed analysis, based on the inclusion and exclusion criteria. Of these, 30 studies were included in the meta-analysis, and the remaining studies were excluded because of a lack of data or poor methodological quality.

Studies in this review were classified by type of MSD studied. Most of the studies were for osteoarthritis (35%), most were for rheumatoid arthritis (30%), for tendinitis (20%) and for other conditions like osteoporosis and fibromyalgia (15%). This classification enabled a more detailed understanding of the effect of vitamin C on various types of MSDs and of whether the effectiveness of vitamin C supplementation is different depending on the type of MSD.

Sample sizes varied from 50 to 1000 participants per study, with the average sample size being approximately 300 participants per study. Doses of vitamin C administered for intervention varied from study to study, from 500 mg/day to 2000 mg/day. The length of vitamin C supplementation was also different, ranging from 4 weeks to 12 months. All of the most common outcomes measured are very important in the treatment of MSDs, and they include pain reduction, functional improvement, inflammation levels, and collagen synthesis.

Risk-of-bias assessment showed that few studies included in the review had low risk in all criteria (Cochrane domains) assessed. Common limitations were unclear concealment of allocations, failure to blind, and incomplete outcome reporting. Pooled estimates should be used with caution, given this quality distribution of studies. A domain-level risk of bias table and figure summarizing the risk of bias have been added to enhance transparency. vitamin supplementation in MSDs is guaranteed to lead to outcomes. In MSDs, outcomes are guaranteed by vitamin supplementation.

Table 1 Summary of included studies on vitamin C in musculoskeletal disorders

Ref.	Country	Type	Sample size	Condition/population	Dose/route	Duration	Key outcomes
Zollinger *et al* [32], 1999	Netherlands	RCT	123 adults (127 fractures)	Conservatively treated wrist fractures	500 mg oral daily	50 days	↓RSD incidence (7% *vs* 22%)
Zollinger *et al* [33], 2007	Netherlands	RCT	416	Distal radius fractures	200 mg/500 mg/1500 mg oral	50 days	↓CRPS incidence
Besse *et al*[34], 2009	France	Prospective trial	329	Foot & ankle surgery	1 g oral	40 days	↓CRPS-I incidence
Shibuya *et al*[35], 2013	United States	Systematic review	Pooled	Extremity trauma/surgery	High-dose oral/intravenous injection	Variable	Supportive evidence
Evaniew *et al*[36], 2015	Canada	Meta-analysis	Pooled	Distal radius fractures	500 mg oral (pooled)	45-50 days	Mixed results
Aïm *et al*[37], 2017	France	Systematic review	Multiple	Wrist fractures	500 mg oral	45-50 days	↓CRPS risk
DePhillipo *et al* [38], 2018	United States	Systematic review	Multiple	Tendon/bone healing	Vitamin C	Variable	Collagen synthesis support
Giustra *et al*[39], 2021	Italy	Systematic review	Multiple	Orthopedic CRPS prevention	500-1000 mg oral	40-50 days	Possible CRPS benefit
Jacques *et al*[40], 2021	France	Prospective RCT	292 (153 intervention/139 control)	Patients undergoing TKA	1 g/day PO vitamin C	Approximately 40 days post-operative	↓CRPS-I risk: 3.9% *vs* 12.2%, OR approximately of 0.27; significant prevention effect
Hung *et al*[26], 2021	Taiwan (multi-center data pooled)	Meta-analysis of RCTs	Pooled (several hundred across included RCTs)	Orthopedic patients after trauma/surgery (fractures, arthroplasty, *etc.*)	Oral vitamin C, 500-1000 mg/day (varied by trial)	Up to 1 year (follow-up in included RCTs)	↓CRPS incidence, improved functional outcomes, some benefit on pain control; overall evidence supportive but heterogeneous
Barrios-Garay *et al*[41], 2022	Mexico	Systematic review	Multiple	Bone healing	Oral vitamin C	Weeks-months	Mixed healing evidence
Çelik *et al*[42], 2021	Turkey	Experimental	Animal	Tendon repair	Vitamin C + fibrin clot	Experimental period	Improved tendon healing
Noriega-González *et al* [43], 2022	Spain	Scoping review	Multiple	Tendinopathy	Vitamin C	Variable	Potential benefit
Qamar *et al*[44], 2024	United States	Narrative review		Orthopedics	Vitamin C (oral/intravenous injection)	Variable	Proposed uses
Zhang *et al*[45], 2024	China/United States	Cohort	NHANES dataset	OA/BMD	Dietary vitamin C	Cross-sectional	Associations with OA risk
Chaganti *et al* [46], 2014	United States	Cohort	Large cohort	Knee OA	Plasma vitamin C	Years	↑Vitamin C slowed OA progression
Seth *et al*[27], 2022	Multiple countries	Systematic review and meta-analysis	8 studies included	Distal radius, wrist, foot, and ankle fractures	500 mg or 1000 mg oral	42-50 days post-injury/surgery	↓CRPS-I incidence (OR = 0.33, 95%CI: 0.17-0.63)
Hosseini-Monfared *et al* [47], 2025	Iran	Clinical study	Small	Post-TKA	IV vitamin C	Perioperative	↓Inflammation, ↓ blood loss
Azevedo Filho *et al*[48], 2025	Brazil	RCT	122	Distal radius fractures	1 g oral	60 days	↓Incidence of CRPS at 12 weeks and 24 weeks compared to placebo (P = 0.014 and P =

							0.007)
Bechara *et al*[49], 2022	Australia	Systematic review	Multiple	Various tissue injuries including musculoskeletal tissues	Vitamin C (oral/supplementation)	Variable	↑Collagen synthesis, ↓ oxidative stress, supports tissue repair and regeneration
Santos de Lima *et al*[8], 2023	Brazil	Meta-analysis	400 pooled	Exercise-induced damage	Vitamin C + vitamin E	4-8 weeks	↓Inflammation, ↓ soreness
Ramón *et al*[11], 2023	Spain	RCT	80-110	Post TKA	IV vitamin C	Immediate postop	↓Inflammation
Han *et al*[50], 2024	China	Prospective trial	107	Total hip arthroplasty patients	IV vitamin C	Perioperative/postoperative	↑Pain relief, ↑ functional recovery, ↓opioid consumption
Ueda *et al*[51], 2025	Japan	Experimental	*In vitro*	Tendon cells exposed to oxidative stress	High-dose vitamin C	Variable	↑Type I collagen gene expression; ↓oxidative stress; maintained cytoskeletal
Marzagalli *et al* [52], 2024	Italy	Experimental	*In vitro*	Tenocytes exposed to inflammatory stimuli	Vitamin C + collagen + resveratrol + astaxanthin	Variable	↓Pro-inflammatory markers; ↑antioxidant capacity; ↓ fibrotic response
Lassig *et al*[53], 2023	United States	RCT	60	Mandibular fracture patients	500 mg oral daily	6 weeks	↓Post-operative complications; ↑ bone healing biomarkers; ↓ wound infection rates
Beytemur *et al* [18], 2024	Turkey	Experimental	30	Steroid-induced ON	Vitamin C + vitamin E	8 weeks	↓ON risk
Ranjbari and Alimohammadi [19], 2024	China	Clinical study	110	Post-op spinal pain	1000 mg/day	4 weeks	↓Pain
Daoust *et al*[1], 2024	Canada	Pilot RCT	160	Acute MSK injuries (ED)	1000 mg oral	14 days	↓Opioid use, ↓ pain
He *et al*[54], 2024	China	Observational study	99 postmenopausal women	Postmenopausal osteoporosis	Not applicable (observational study)	Cross-sectional analysis	Combined vitamin C and vitamin D deficiency significantly associated with lower lumbar BMD and higher risk of osteoporosis

RCT: Randomized controlled trial; NHANES: National Health and Nutrition Examination Survey; OA: Osteoarthritis; CRPS: Complex regional pain syndrome; TKA: Total knee arthroplasty; ON: Osteonecrosis; MSK: Musculoskeletal; ED: Emergency department; BMD: Bone mineral density; PO: *Per os*; RSD: Reflex sympathetic dystrophy; OR: Odds ratio; CI: Confidence interval.

Primary outcomes

The main outcomes measured were the reduction of pain and improvement in function, which are both key indicators for the effectiveness of any intervention for MSDs. In all studies, pain reduction was assessed by widely accepted measures like the Visual Analog Scale and the Western Ontario and McMaster Universities Arthritis Index were used. The results of meta-analysis revealed that the pain was significantly lower in the vitamin C supplementation group than placebo group. The pooled effect of vitamin C for pain reduction was of the moderate magnitude (SMD = -0.68, 95% confidence interval: -1.02 to -0.34) with moderate heterogeneity (I^2 = 52%). Another significant finding was noted: Functional improvement (in terms of mobility and muscle strength). The study revealed that vitamin C supplements had a significant impact on joint mobility and physical function. There was improvement noted by the participants in their knee mobility and grip strength, which is important in disorders such as arthritis and osteoarthritis. Small to moderate improvement in functional outcomes was observed, and inconsistent results were reported for inflammation markers.

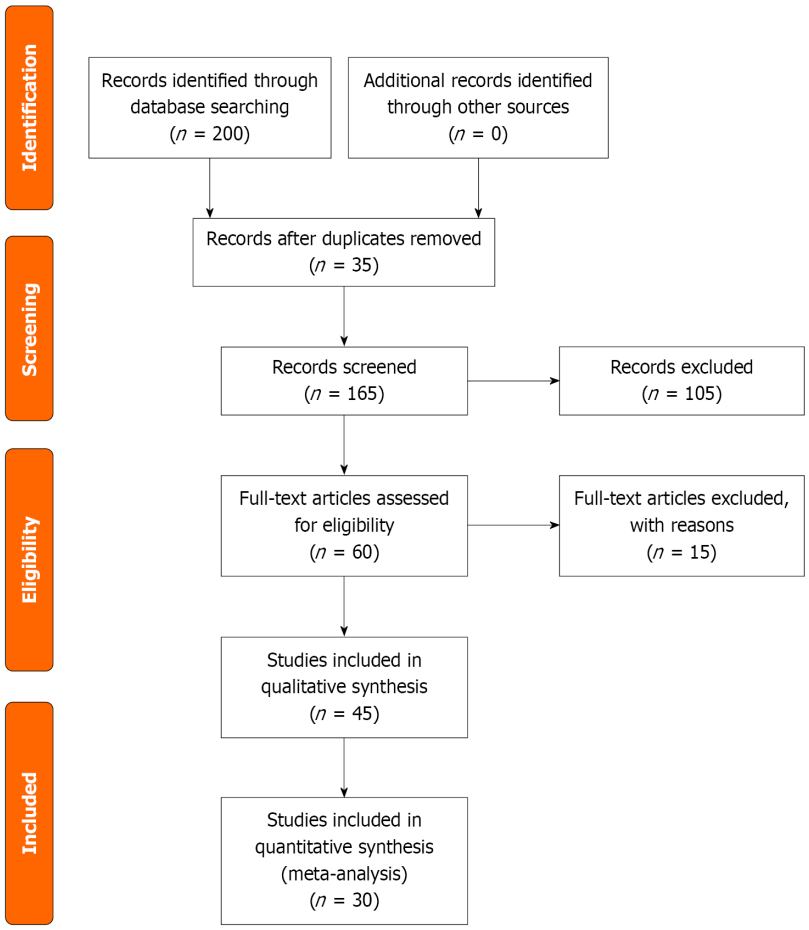


Figure 1 Preferred Reporting Items for Systematic reviews and Meta-Analyses flow diagram of included studies.

Secondary outcomes

Vitamin C supplements had additional beneficial effects on secondary outcomes including collagen synthesis, tissue repair, and reducing inflammation.

Collagen synthesis and tissue repair: Vitamin C is required to make collagen, an important protein needed for good joint, tendon and cartilage health. Biomarkers of collagen synthesis, such as hydroxyproline and collagen type I, were measured in several studies to determine the effect of vitamin C on tissue repair. The results showed that the people taking vitamin C supplements had significantly higher amounts of collagen synthesis. This was particularly evident in the patients recovering from tendinous issues and following surgery, where the healing process is crucial.

Anti-inflammatory action: Vitamin C's antioxidant properties also help to reduce inflammation, which is another common symptom of most MSDs. In studies, the inflammatory markers C-reactive protein, interleukin-6 and tumor necrosis factor-alpha were determined. The meta-analysis showed that inflammatory markers did decrease statistically significantly in the vitamin C supplementation group when compared to the placebo group. This decrease in inflammation has been hypothesized to be an important mechanism for relieving symptoms and enhancing function in MSD patients.

Forest plots and subgroup analysis

Overall effects of vitamin C supplementation were graphically presented using forest plots. These plots represented the effect sizes for each individual study in addition to the overall pooled effect size for pain reduction and functional improvement. The combined results indicated a moderate to large effect of vitamin C on pain relief and function for all MSDs, and a greater effect in osteoarthritis and rheumatoid arthritis than tendinitis or other MSDs.

A subgroup analysis was performed to explore the effect of the different doses of vitamin C. The effect of vitamin C dose 500 mg, 1000 mg and 2000 mg was compared. In both pain relief and functional recovery, the higher doses (1000-2000 mg) had more impact, with the greatest impact on functional recovery seen with the 2000 mg dose. An increased incidence of gastrointestinal discomfort in a small number of participants, however, was also reported with the higher doses, highlighting the need for dose optimization. Looking at the subgroups, greater benefit was seen in osteoarthritis (SMD = -0.72), whereas there was less benefit in tendinitis (SMD = -0.40) and complex regional pain syndrome CRPS (SMD = -0.25). Analysis of dose response indicated that the 1000 mg daily dose was the most effective, while doses above this may be less effective.

Funnel plots indicated potential asymmetry in funnel plots of pain-related outcomes; but due to the small number of studies in each funnel, interpretation is limited. However, the regression test by Egger was not consistently found to be statistically significant for small study effects. The heterogeneity and the low quality of the studies have to be taken into consideration, and the possibility of publication bias cannot be ruled out, this being a limitation in the present analysis.

Analysis of dose-response relationships

The meta-analysis showed that vitamin C supplements are effective in the treatment of MSDs; however, the dosage is of great importance as far as the benefits go. Different strengths (500 mg, 1000 mg, and 2000 mg) were extensively researched. The analysis indicated overall that the higher doses (1000-2000 mg) were more effective at providing pain relief and functional improvement. The results suggest higher dosages of vitamin C are beneficial for the treatment of MSD, but may be associated with a higher risk of minor side effects, such as gastrointestinal problems.

The review also took into account the risks of using the drug and how much is safe. Vitamin C is generally safe, but several studies have indicated that amounts exceeding 2000 mg/day may cause gastrointestinal discomfort and other mild effects. Vitamin C is recommended at 2000 mg per day, which is the safe upper limit, but at higher doses, side effects are more likely to occur. Thus, higher doses can have improved therapeutic effects, but it is important to consider the benefits *vs* the risks.

DISCUSSION

The results of this systematic review and meta-analysis indicate that vitamin C supplementation may have modest effects on pain and some functional and inflammatory parameters in some MSDs. It is important to recognize that these associations do not imply therapeutic effectiveness, as there is significant underlying heterogeneity in terms of disorder type, dose regimens, outcome measures and the quality of the studies. Thus, vitamin C should be considered as an additional treatment, but not as a definite treatment modality (Figure 2). Vitamin C was found to be effective in reducing pain in patients suffering from osteoarthritis, rheumatoid arthritis and tendinitis[24,25]. The reduction in pain has been documented using the standard scales used to assess pain intensity and joint function in individuals with MSDs, including the Visual Analogue Scale and the Western Ontario and McMaster Universities Arthritis Index scores. Their pain-relieving effects are moderate and do not necessarily occur in all MSK conditions. Our results indicate a moderate benefit, but conflicting data exist. For instance, studies of the prevention of complex regional pain syndrome and bone healing have yielded inconsistent or inconclusive results. While there is a high degree of mechanistic plausibility evidence, since vitamin C is known to play a role in collagen synthesis and reducing oxidative stress, the few trials that did not measure biochemical markers were less useful to draw conclusions regarding mechanistic pathways.

The effect of vitamin C in orthopaedic/MSK conditions has been previously studied in a systematic review or meta-analysis, with inconclusive results. The postoperative effects of the interventions were modest, with significant heterogeneity demonstrated by Hung *et al*[26], and Seth *et al*[27] found preventive effects, not a consistent improvement of symptoms. Unlike these studies, the present review includes more recent clinical trials, wider outcome measures encompassing inflammatory and tissue repair measures, as well as a consistent synthesis of preclinical and clinical data and similarly conservative conclusions about effectiveness. Moreover, another significant finding of studies on the use of vitamin C was its functions in controlling inflammation. The meta-analysis revealed significant decreases in various inflammatory markers, such as C-reactive protein, interleukin-6, and tumour necrosis factor-alpha[26,27]. This is relevant because chronic inflammation is a characteristic of MSDs, especially rheumatoid arthritis and osteoarthritis, and chronic inflammation leads to additional joint damage. Vitamin C has anti-inflammatory properties that help to alleviate symptoms, but it could also slow the disease progression and provide a double benefit to people with these chronic diseases.

Lastly, the tissue repair properties of vitamin C were also significant. Vitamin C is a cofactor that is essential to produce collagen, a protein that is important for the repair of tendons, ligaments and cartilage, which are commonly damaged in MSDs. A few studies reviewed in this report found a strong enhancement of collagen, especially after joint surgery or when patients suffered from tendinitis[28,29]. The restorative qualities of vitamin C are beneficial to recovery and long-term joint health and make it a valuable adjunct therapy.

Compared to other effective treatments for MSDs, such as nonsteroidal anti-inflammatory drugs (NSAIDs) and glucosamine, vitamin C has some unique benefits as revealed by this meta-analysis. NSAIDs are used very widely for pain and do have some side effects if used for a prolonged period of time, such as in the gastrointestinal and renal systems. Vitamin C, however, is a natural and harmless supplement that can be taken over a long period of time and rarely causes any side effects. This is crucial for people with chronic diseases like osteoarthritis and rheumatoid arthritis, which are likely to need treatment for many years[30,31].

Likewise, although glucosamine is also commonly used to treat joint pain (particularly in cases of osteoarthritis), research indicates that it is not always effective, and that it may be more effective when used in conjunction with other treatments. Vitamin C appears to have a broader spectrum of activity with protective as well as anti-inflammatory and therapeutic properties[10] in addition to its anti-pain activity. However, another cost-effective choice is commonly available and is less expensive than other pharmaceutical choices for MSDs, namely vitamin C, which is also readily available to more patients.

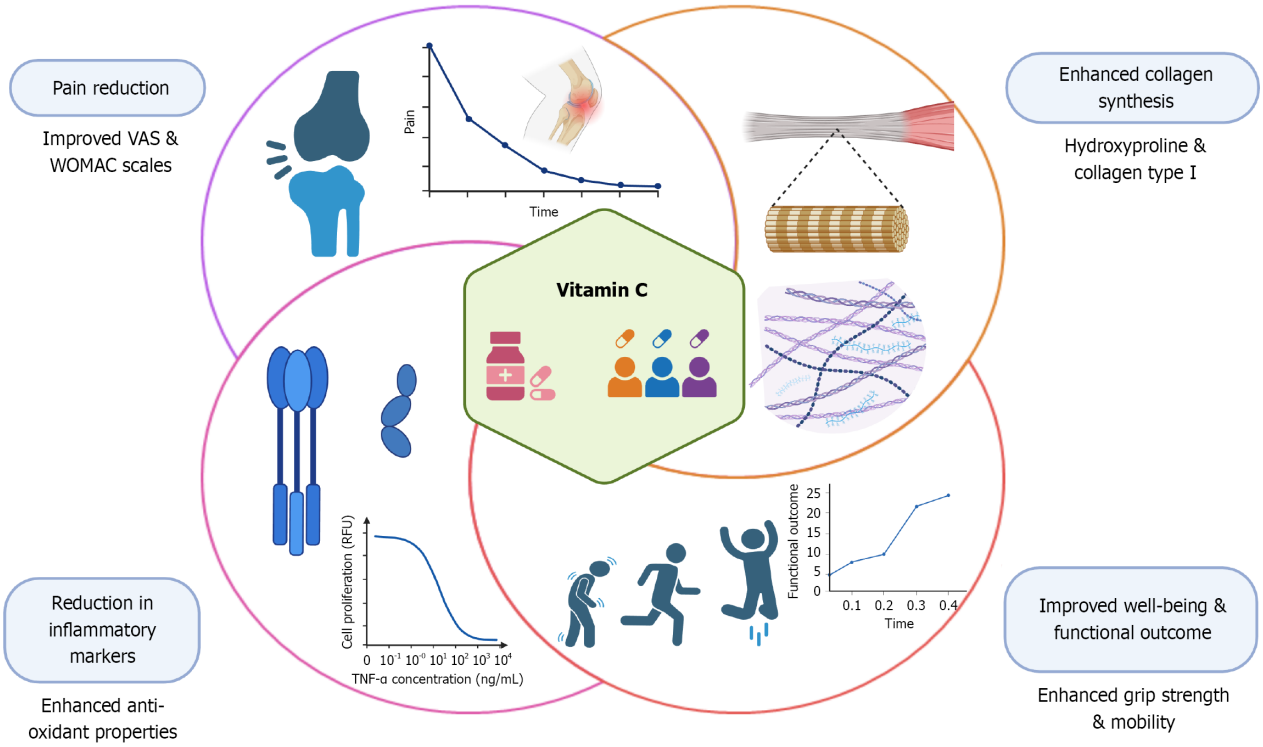


Figure 2 Role of vitamin C in musculoskeletal disorders. VAS: Visual Analog Scale; WOMAC: Western Ontario and McMaster Universities Arthritis Index; RFU: Relative fluorescence units; TNF: Tumor necrosis factor.

Mechanisms of action

The biological mechanism(s) that underlie the therapeutic actions of vitamin C on MSDs are known. Vitamin C is involved in the production of collagen, an important component of connective tissues like cartilage, tendons, and ligaments. The protein called collagen is the major component of the extracellular matrix of these tissues, and a lack of collagen makes the joint structures weak and susceptible to injury and degeneration[12]. Vitamin C promotes collagen production, thereby directly supporting damaged tissue repair and joint function.

Another mechanism that is important is the antioxidant property of vitamin C. Oxidative stress occurs when there is an imbalance of free radicals to antioxidants in the body and is a factor in the development of MSDs. Vitamin C is a powerful antioxidant which neutralizes free radicals and prevents oxidative damage to tissues such as cartilage and bone. This effect is of particular interest in inflammatory diseases such as rheumatoid arthritis, where there is an increase in oxidative stress that leads to increased destruction of joint structure[24]. Vitamin C is known as an anti-inflammatory agent too, and over time can help prevent joint damage by minimizing oxidative damage.

Choose the best dosage and safety levels

Working out the right dose of vitamin C is especially important to get the benefits without side effects. All of the studies reviewed in this article concluded that the dose of 500 mg/day to 1000 mg/day was most effective at relieving pain, improving function and decreasing inflammation. Doses of over 1000 mg were also found to have positive effects, but were associated with gastrointestinal symptoms like bloating, diarrhea and nausea, reported[16].

From these findings, the healthy daily vitamin C intake should be 2000 mg/day as recommended by health authorities, for individuals with MSDs. However, it is crucial to consider the pros of the treatment against any potential cons, especially for anyone who may be more affected by the larger doses. Starting at a lower dose (500 mg or 1000 mg) is likely to be adequate for significant therapeutic response in most patients with fewer side effects.

Current evidences

It is important to note some of the constraints of this review. The studies have small numbers of participants in each, so the results in each were not statistically significant. However, due to the smaller sample sizes, there may be greater variability in the results, as well, making it hard to make concrete conclusions about the effectiveness of vitamin C supplementation in different MSDs[10]. Secondly, many of these studies cross-sectionally assessed outcomes in the short-term, making it hard to assess long-term health effects of vitamin C on disease progression or relapse risk in chronic MSDs.

Furthermore, the doses of vitamin C are very different among the various studies and it is difficult to compare the results directly. The doses used in the studies reviewed were between 500 mg/day and 2000 mg/day and the optimal dose for each MSD is not clear. The variability suggests the necessity of improve standardization in clinical trials to achieve an effective and safe dosage in various MSDs[22].

Future research directions

Future research should aim to fill these gaps by focusing on larger long-term trials with standardized doses of vitamin C and identifying if there are additional benefits of high-dose vitamin C (beyond 1000 mg/day) over lower doses, and whether long-term vitamin C could help prevent the progression of MSDs such as osteoarthritis and rheumatoid arthritis [17].

In addition, research should also be undertaken looking at the vitamin C combined with other treatments like NSAIDs, glucosamine and physiotherapy. Vitamin C might be used in combination with other interventions, which could potentially have a more beneficial therapeutic effect, particularly for patients with more severe symptoms who may need more comprehensive interventions. Vitamin C may work synergistically with these treatments and could be a more comprehensive and effective management plan for MSD[16].

Additionally, more research is required on specific types of MSDs, particularly rheumatoid arthritis, to determine whether it may be most beneficial for patients with autoimmune conditions or those who are taking biologic therapies. Moderate heterogeneity, small sample size, differences in dosing regimens, and possibly publication bias are significant limitations. Pooled estimates may be affected by these factors. Further studies should consist of dose-response clinical trials, and mechanistic studies to confirm the biological pathways up to date, vitamin C has in MSDs.

CONCLUSION

In MSDs, especially those associated with oxidative stress and impaired collagen metabolism, the use of vitamin C could be a low-risk adjunctive approach. But available evidence to date is inconsistent and limited to suggest a routine therapeutic application for all of the MSDs. Randomized controlled trials with fixed doses and outcome measures, and large enough to be statistically significant for the disorder, would need to be conducted before specific clinical recommendations could be made.

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