

Vitamin C and Osteoarthritis Pain-Modulation

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Abstract

Osteoarthritis, a painful irreversible disabling joint disease and one that predominantly affects articular cartilage is rapidly increasing in prevalence among older populations. This overview aimed to examine whether: 1) vitamin C, a powerful antioxidant involved in many physiological processes can influence the pain experience of osteoarthritis and 2) more research in this realm should be undertaken. A comprehensive overview of relevant English language research reports published over the last 30 years revealed no clear conclusion as regards the key study question. However, given some evidence favoring a possible protective, reparative or mediating role for vitamin C in the context of osteoarthritis pain, which remains largely impervious to effective long-term remediation, further research appears warranted.

Keywords: *Articular Cartilage; Ascorbic Acid; Osteoarthritis; Pain; Vitamin C*

Introduction

Painful disabling osteoarthritis, the most prevalent joint disease, remains highly impervious to effective amelioration in response to current non-pharmacologic treatment approaches such as exercise, weight loss, physical aids and education, despite years of usage and research in this regard. Moreover, several pharmacologic treatment approaches employed to offset osteoarthritic pain fail to modify the disease and its progression to any known degree. They may well be contraindicated for long-term use due to their often toxic or fatal side effects [1], the possible increased risk in terms of cardiovascular disease posed by several anti-inflammatory drugs, such as corticosteroids [2], cerebex, or tramadol [3] as well as being at potential risk for adverse health outcomes following injections of various sorts [4]. In addition, some recently tested biologically oriented therapeutic approaches have similarly failed to slow the rate of osteoarthritis joint space narrowing and/or were withdrawn before study completion in some cases [5,6], certain anti-inflammatory drugs have been shown to hasten, rather than slow the disease process, or to impact joint space narrowing, but not pain [5]. Moreover, most treatment approaches for osteoarthritis, even if independently efficacious, often neglect to consider the complexity of the disease and its impact on, along with the involvement of, surrounding joint tissues, as well as its multifaceted cognitive and metabolic correlates. Additionally, its molecular and biomechanical pathogenesis is often discounted in the context of attempts to both understand the sources of, as well as the means of alleviating osteoarthritis pain [2,5]. On the other hand, a strategy that can influence the structural and functional properties of articular cartilage and surrounding bone, as well as the surrounding muscles and nerve supply, plus inflammation in a positive way, while safeguarding or helping to foster overall physical and mental health, would be highly valuable in the context of pain relief or the prevention of excess pain, the symptom of most concern to osteoarthritis patients.

In this regard, vitamin C, chemically identified as ascorbic acid, is a well-established anti-oxidant with biological proven tissue-based impacts, such as playing an essential role in collagen formation [7], one of the main components of cartilage [8], as well as having broader neurological effects [9] crucial to the maintenance of the skeleton and possibly to its associated tissues and body systems [2]. Moreover, its ability to foster multiple enzymatic processes and decrease inflammation, while influencing bone metabolism favorably is likely to be more helpful than not in preventing or attenuating osteoarthritis disease processes and their negative painful and disabling consequences.

Aims

In light of the immense global burden of painful osteoarthritis, an incurable disabler of many aging adults, this review aimed to specifically examine the extent of support for the idea that vitamin C, an established mediator of tissue biology, growth and development with powerful anti-oxidative and anti-inflammatory properties [10] may be an influential modifiable factor in the context of efforts to minimize, modulate or mediate osteoarthritis pain. A secondary aim was to establish whether further research appears warranted in this realm given the burden of the disease and the purported role vitamin C plays in collagen synthesis and many key enzymatic essential life-affirming biological processes, as well as metabolic and neurological processes, implicated in osteoarthritis, an idea disputed by several researchers [11-20], but not all [21-25].

Methods

To achieve these review aims, an extensive review of available documents housed in PUBMED and Scopus from 1990 up until August 31, 2019 using the key terms Vitamin C and Pain, or Ascorbic Acid and Pain and/or Osteoarthritis was undertaken.

To this end, all articles on these websites were scanned for relevance and salient research articles or reviews that addressed some aspect of the current topic of interest were then reviewed in more depth without regard to research design. An attempt was made to include all modes of experimentation, but the focus was on clinically derived data as vitamin C is synthesized by almost all animals used in preclinical osteoarthritis studies. No systematic review was conducted and while it is acknowledged the body of data may not be exhaustive-it does arguably highlight some telling lines of research and tentative conclusions and uses two data bases presumably believed to house state of the art and gold standard papers on this topic sufficient for arriving at a reasoned opinion through a narrative lens.

Results

As of August 2019, the data examined revealed only a small number of relevant studies, if compared to other themes in osteoarthritis research. For example, the search terms 'vitamin C and osteoarthritis pain', yielded 27 references in PUBMED with 480 listings for the terms 'pharmacologic drugs and osteoarthritis pain'. In the context of 'surgery and osteoarthritis pain' there were 11383 reference sources dating back to the 1970s. This small number of vitamin C related studies included a limited number of pre-clinical studies, along with largely cross-sectional clinical research reports and review articles, but with no unifying or consistent theme. Indeed, diverse observations, including some focusing on deficiency effects of vitamin C in osteoarthritis, some on its possible pain relieving or provoking supplementary effect and some on its anti-oxidant or pro-oxidant effect, were evident and highly contradictory or opposing conclusions were more common than anticipated given findings of many preclinical observations and those in other clinical diseases. As well, challenges in identifying the sources of vitamin C discussed in some clinical studies, as well as the failure to employ adequately reliable measures of vitamin C status, along with highly heterogeneous osteoarthritis samples, must assuredly render the strength of any emergent relationships between vitamin C and osteoarthritis pain tentative at best.

However, there seems to be little argument and a general consensus that vitamin C is an important antioxidant and co-factor for numerous biochemical reactions [19] especially those involved in the synthesis and assembly of cartilage collagen [8,25,26], aggrecan and proteoglycans [27], which are key constituents of articular cartilage [28-32]. Vitamin C is also an important factor in mediating

general wellbeing, such as cardiovascular and neurological health, often found impaired in people with chronic osteoarthritic pain. As well, inflammatory mediators, as well as inflammation that accompanies osteoarthritis causing joint destruction and pain [10], along with chondrocyte damage, may be significantly reduced in the presence of adequate dietary and/or supplementary levels of vitamin C [8,21,33,34], as may complex regional pain [35,36].

Other research shows skeletal muscle, highly implicated in osteoarthritis pain and pathology [37] and an important storage site of vitamin C [38,39] may atrophy in the presence of a vitamin C deficiency [40] and that in addition, the width of an osteoarthritic joint may be impacted by the degree of available vitamin C [41].

Other data show that although scurvy a disease caused by a vitamin C deficiency is not analogous to osteoarthritis, its highly similar pain and mobility features can be reversed with vitamin C supplementation. Yet other research shows vitamin C, an essential cofactor for fostering collagen linkage production, ligament, tendon and bone quality [42] is often present at marginal levels in people with arthritis, especially, if multiple drugs including painkillers and anti-inflammatory drugs, are being used [23,38]. As well, clinically relevant associations are found to exist between vitamin C and spinal pain, a common osteoarthritis complaint [42], as well as for pain and vitamin C in selected osteoarthritis patients.

In terms of explaining how vitamin C can reduce osteoarthritic pain, Chiu, *et al.* [43] found that this vitamin helped to decrease, rather than increase, apoptotic processes as well as the expression of pro-inflammatory cartilage chondrocyte cytokines and matrix metalloproteases, even at low doses, a finding also noted by Ibold, *et al.* [44]. Early work by Davis, *et al.* [22] who attempted to determine the influence of vitamin C on locally induced inflammation and arthritis in rat paws, further showed that daily subcutaneous administration of 150 mg/kg of vitamin C over 20 days reduced arthritic swelling, as well as leukocyte infiltration, while increasing pain tolerance. Another possible mechanism involves an initial reduction in chondrocyte lysosomal enzyme activity and thus less extracellular matrix breakdown [28]. Another is the prevention of oxidative injury and deterioration of associated musculoskeletal deficits [45] and widespread pain [35], while possibly serving as a key influence in regulating extracellular cartilage matrix stiffness and homeostasis [7].

However, the desired vitamin C levels needed to foster or maintain joint integrity may be adversely affected by analgesics [38], as well as by dysfunction in the cellular transporter mechanism necessary for vitamin C utilization by the articular cartilage cells and others that may partially control their gene activity [26,30,46]. Other related side-effects of this latter situation are a possible reduction in the desired intestinal ability to absorb vitamin C effectively, even if intake is considered optimal, which could be problematic given that some cases with knee osteoarthritis who have significantly decreased serum or plasma vitamin C levels appear to experience more significant adverse radiographic changes [8,27] than those with adequate levels, even if this is not a universal finding. On the other hand, having adequate vitamin C intake levels may produce a possible protective role in this regard [41,47-51]. Antioxidant micronutrients, including vitamin C, may also help to reduce inflammation, an important pain determinant [52], while reducing pain attributable to bone-related changes [53,54].

A further body of research implies that the presence of sufficient levels of vitamin C may also promote tendon and muscle collagen synthesis, while improving the antioxidative capacity of the synovial fluid, all possible structural changes that could lower the degree of any existing osteoarthritis pain [34]. On the other hand, minimizing any risk of a vitamin C deficiency may not only help to abate pain, but may impact favorably on obesity, as well as depression [55], strongly linked to osteoarthritis pain [56], while decelerating the disease progression [34]. In other instances, cases recovering from fractures and surgery may experience a lower risk of acquiring regional pain syndromes [35], adequate levels of vitamin C intake may impact favorably on articular cartilage measures of viability [57], while decreasing prevailing doses of needed analgesics [38] and preventing the negative impact of reactive oxygen species on the production of intractable osteoarthritis pain [58].

Discussion

Osteoarthritis, a highly disabling incurable joint disease and one where any form of palliative or reparative treatment that is non-toxic and encourages mobility, while reducing pain, would be highly prized, remains largely subject to pharmacologic and/or surgical interventions of varying degrees of efficacy and effectiveness. In this regard, despite considerable background research on the importance of vitamin C in minimizing oxidative stress, for example that found in osteoarthritis, very little research has been forthcoming in the realm of applying vitamin C associated research towards understanding osteoarthritis pain and its possible reduction or prevention via vitamin C, despite several well-founded reasons for considering this possibility.

That is, despite a reasonably strong underlying rationale for believing that vitamin C is an important daily requirement for purposes of ensuring optimal joint health and that persons with osteoarthritis may be at risk for either a reduced ability to take up vitamin C or have a greater need for this vitamin than those who are not subject to inflammatory joint changes, the possibility that suboptimal vitamin C levels are related in some way to the presence of osteoarthritis pain and its severity and extent is not only poorly studied, when compared to other topic areas that have not been fruitful, but continues to be reported as potentially unsafe, or to possibly do more harm than good, or alternately to have no clinical benefits among people with osteoarthritis or at risk for this disease [12]. In addition to that, what is published is often reliant on subjective or semi quantitative outcomes, as assessed on one occasion, or over time, without any stringent control strategies, or use of available biotechnological tools and experimental approaches that examine cellular and molecular levels of influence.

This seems unfortunate because vitamin C has been studied for many years, from many perspectives in its own right and as a result, several authors have noted a potentially valuable role for considering the possible role of vitamin C in mediating or moderating the highly resistant form of pain experienced by people with osteoarthritis. The possibility of vitamin C as an adjunct for alleviating, minimizing, ameliorating, or treating osteoarthritis joint damage, which may stem from multiple sources has also been discussed, for example as a possible dietary intervention [59,60], or as a significant add on intervention in the context of analgesic therapy [58]. Vitamin C also possesses multiple capacities for prevention of osteoarthritic progress, including a decrease in apoptosis and the expression of pro-inflammatory cytokines, in addition to its well-known antioxidative effect [13].

However, to more ably address design shortcomings and resolve the presently divergent viewpoints concerning the safety of vitamin C, along with other issues that emerge from these studies and explore uncharted avenues, such as the value of vitamin C in neuromodulation [9] and metabolic syndrome and obesity [60], as this pertains to osteoarthritis pain, it is clear more creativity as well as carefully designed rigorous prospective research and innovative research questions and methods are strongly indicated. In particular, designs with adequate power and clear inclusion criteria, that can minimize several known methodological shortcomings in this line of inquiry, such as reliance of food frequency questionnaires or self-reports and failure to assess actual total intake plus plasma levels of vitamin C and pain at regular intervals [24,50] will be extremely valuable in all likelihood. In addition, even if valid instruments are applied, the heterogenous nature of osteoarthritis implies that studies designed to identify and disaggregate osteoarthritis subgroups, rather than failing to do this, will be highly valued as well. Careful attention to assessing dose concentration relationships between vitamin C supplements, dietary intake and pain as well as functional correlates of various osteoarthritis cases in both the clinic and in research realms over extended periods is also indicated to help ensure that clinically meaningful relationships are able to emerge and be demonstrated. At the same time, clearly delineated baseline demographics, plus data depicting levels of prevailing oxidative stress, inflammation and pain, as well as nutritional practices, comorbid disease status, medication intake, the nature of any supplementary osteoarthritis treatments, along with adequately blinded subjects are desirable in in supplementary related trials and others.

In the interim, since vitamin C is clearly an essential co-factor for fostering normal collagen synthesis, including collagen X [61,62], a major structural element of articular cartilage and its surrounding tissues [63], as well as for other vital physiological functions [7],

including those that may be compromised in osteoarthritis, it seems reasonable to suggest that prevailing levels of this vitamin should not be overlooked as a potentially important and salient pain related factor in selected osteoarthritis cases. The fact that deficient vitamin C levels are also associated with pain provoking inflammation that often accompanies osteoarthritis [64], along with evidence that there are vitamin C transporter deficiencies that would markedly impact cartilage cell stimulation and cartilage collagen production, matrix formation and assembly adversely [30,65,66] a role for vitamin C in osteoarthritis pain production cannot be ruled out readily. The additional research pointing to parallel alterations in the structure and function of muscles, tendons, ligaments, nerves and bone structures surrounding the osteoarthritic joint in the presence of vitamin C insufficiency, further strengthens the potential salience of future research efforts in this regard by those interested in examining and preventing osteoarthritis pain and its ramifications. Indeed, new research shows that the administration of 500g of vitamin C twice in the case of foot and ankle trauma not only helps to reduce related analgesic requirements, but also improves pain scores and helps subjects achieve better functional outcomes. In another related report, the authors noted that individuals without baseline osteoarthritis who self-report vitamin C use, are less likely to develop the disease than those who do not [24].

Other data have further shown osteoarthritis progression and the risk of developing knee pain is influenced positively by vitamin C intake doses [67], back and joint pain, often hard to attenuate, can potentially be alleviated by the simultaneous delivery of calcium ascorbate and collagen supplementation [68] and vitamin C can serve as an important antioxidant against systemic stress [65]. Vitamin C derivatives can also be expected to offset inflammation, including that found among obese cases of osteoarthritis [59], while preventing or decreasing disease associated oxidative stress [65,69] that can provoke pain in this disease [60] through multiple pathways. As well, surgery for osteoarthritis or joint injuries may be optimized and any associated bone dysfunction as well as muscle dysfunction may be minimized or prevented in the presence of optimal vitamin C levels [35].

At the same time, the conclusion implied by Chaganti, *et al.* [17] and Li, *et al.* [15], namely, that high levels of vitamin C are more likely to be positively associated with more severe, rather than less severe joint destruction, clearly needs more thorough study. However, since this research did not account for the fact that those with highly destructive osteoarthritis may not be able to transport and utilize available sources effectively [30], even though there may be a demand for supply of this nutrient, the claims made by this group in this regard should be studied more intently. An alternate possibility is that more severe cases of incident osteoarthritis may be exposed to excessively harmful levels of anti-inflammatory or analgesic medications and their negative effects on osteoarthritic joints. Another is that having not been treated sufficiently for pain, their sedentary status and vitamin C transporter dysfunction combined with a reduced ability to absorb vitamin C at an optimal rate [59], may impact the extent of the prevailing joint pathology more negatively than anticipated.

Moreover, fatigue, joint swelling, muscle aches and pains, bone alignment and emotional changes [53], mood instability and diminished stress resilience [70], obesity [4], cardiovascular disease [71] and diabetes, all highly important symptomatic correlates of osteoarthritis pain may independently contribute to the overall magnitude of radiographically defined pathology, regardless of prevailing vitamin C levels. By contrast, it is also possible that the presence of high levels of vitamin C may actually relieve inflammatory damaging pain sources [75] and this possible impact on decreasing superoxide dismutase production permits patients to overload their joints unless warned not to do so, hence producing more joint damage than anticipated. Since the antioxidant properties of vitamin C may only emerge after prolonged administration [33] and according to Duarte and Lunec [72] most studies they reviewed showed either a vitamin C-mediated reduction in oxidative DNA damage or a null effect, whereas only a few showed an increase in specific base lesions, efforts to more carefully examine these interactions is clearly desirable. In addition, research to examine the possible link between the prevailing joint damage due to osteoarthritis and the vitamin C transporter mechanism and if this can be favorably influenced to foster vitamin C transportation into chondrocytes and other joint tissues may prove highly beneficial in the context of pain. Its specific role in fostering the mechanical properties of articular cartilage, bone, tendon and muscle, while positively affecting neural transmission, which has not been well-studied should also be explored on a longitudinal basis in this regard.

Meantime, more evidence than not, implies the presence of a persistent vitamin C deficiency found to be debilitating generally speaking, may be one factor that inadvertently raises the risk for osteoarthritic joint changes, as well as for accelerating or magnifying any prevailing joint destruction and with this the degree of persistent pain found in this patient population. In addition, even though the idea that doses of vitamin C above recommendations should be avoided, Bendich and Langseth [71] found no consistent evidence for negating the long-term consumption of higher than recommended levels of vitamin C, even if a negative role for excess vitamin C cannot be ruled out. By contrast, the addition of extra ascorbic acid to the diet may help to mitigate the onset as well as the progression of the disease [73], while decreasing the need for long-term analgesia [74], especially in cases with other health problems, even if this idea is refuted by Hung, *et al.* [11]. To generate more insight into this issue and others and to foster more adequate translation of prevailing data to the clinic however, the present literature plus the possible linkages presented in figure 1 applied to osteoarthritis sub-groups with and without verifiable oxidative damage might serve as a reasonable starting point. After that, meticulously and rigorously designed studies to rule out competing hypotheses and to avoid cross sectional inferences that do not take into account the fact that reported vitamin C intake may not be the same as actual plasma levels and that its effects may be both disease specific, as well as dose-dependent and take weeks or months to unfold [59] are advocated. The efficacy of tailoring doses for reducing osteoarthritis pain and moderating its development should also be examined.

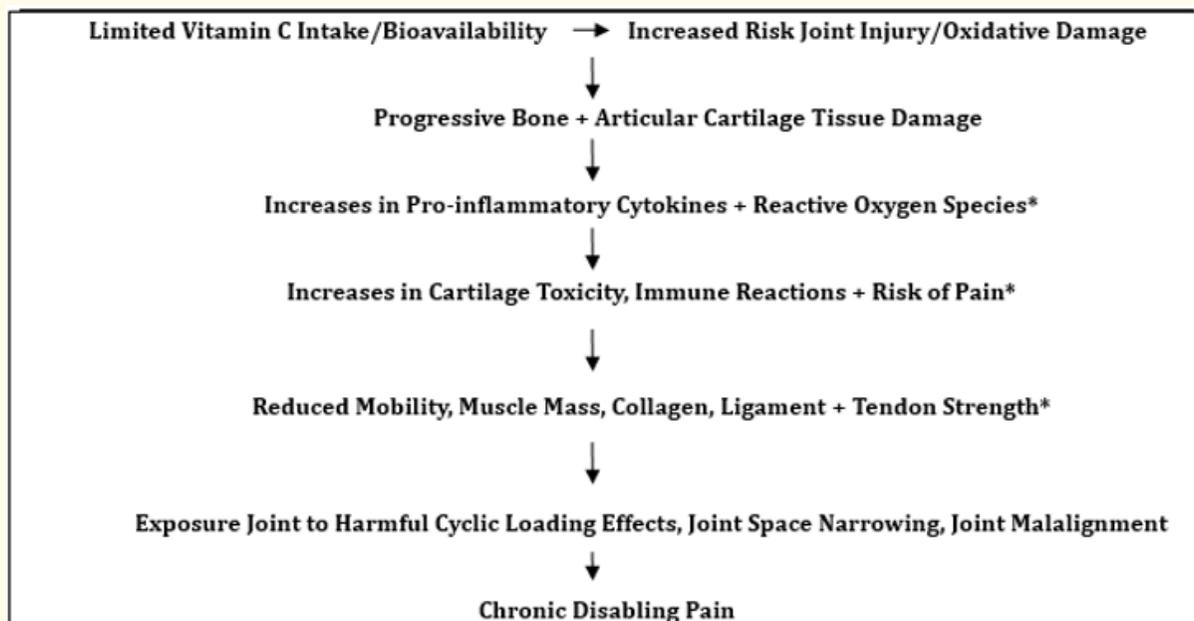


Figure 1: Points* at which vitamin C or a lack thereof may influence the osteoarthritis pain cycle.

Conclusion

In 2012, Bennell, *et al.* [91] posed the question of whether researchers could possibly identify an effective and safe pain-relieving modality in the context of knee osteoarthritis. Based on this current mini review and in agreement with Hart, *et al.* [92], Jensen, *et al.* [93], French and Clegg [94], plus Riffell, *et al.* [95], it seems reasonable to conclude that osteoarthritis pathology and its pain, whether at the knee joint or other joints, may be influenced in a multitude of ways by the presence of varying levels of vitamin C [76,96] even if not favorably in all instances [97,98].

However, even though the limited evidence-base points more soundly to the fact that joint injury and unrelenting osteoarthritis pain is more likely to occur in the presence of deficient levels of vitamin C, than an excess of vitamin C, the impact of varying vitamin C levels on osteoarthritic pain remains to be proven more substantively [99,100]. Since a consistent vitamin C deficit can negatively influence collagen production and inflammation control, as well as oxidative reactions, while its carefully construed administration is found to yield multiple potential pain-reducing benefits, the nature of these associations and others not highlighted in table 1 should be rigorously examined in clinical settings, including the differential impact of various forms of application and dosages and their longitudinal influence on joint structure, biomarkers of pain, as well as function and possible efficacy when compared to collagen supplementation alone, as well as other pain relieving nutraceuticals not reported here [101,102]. Methods of delivery that need to be studied with rigor in their own right are shown in box 1.

- Beverage supplements
- Dietary fruit and vegetable sources [77]
- Freeze-dried dietary powders [60]
- Freeze-dried beverages
- Intra-articular injections [4]
- Intraperitoneal administration [75]
- Intravenous infusions [37,79]
- Iontophoresis using continuous electric current [49]
- Oral supplements of varying dosages, combinations, formulae, and usage instructions
- Topical applications [83]
- Vitamin C enriched diet [27] and fruit consumption [89]
- Laser facilitated transdermal delivery [95]

Box 1: Modes of Delivery Examined in Vitamin C Research that Could Impact Osteoarthritis Pain Outcomes and that Could Serve to Accomplish Optimally Desirable Vitamin C Bioavailability.

Researchers	Key findings
Aim., <i>et al.</i> [77]	Reduces complex regional pain states
Azizi., <i>et al.</i> [78]	In association with growth factors accelerates articular cartilage repair
Ballaz., <i>et al.</i> [9]	May potentiate the anti-nociceptive effects of opioids, and other analgaesics
Burger., <i>et al.</i> [54]	May help to expand subchondral bone osteoblasts while maintaining their special cellular characteristics
Chiu., <i>et al.</i> [43]	Possesses multiple capacities for preventing osteoarthritis progress
D'Aniello., <i>et al.</i> [7]	Regulates extracellular matrix/collagen homeostasis
Han., <i>et al.</i> [80]	Intake of whole fruits and vegetables may improve knee pain in older adults
Huang., <i>et al.</i> [32]	May enhance the anticatabolic effects of hyaluronic acid on osteoarthritic chondrocytes
Iannitti., <i>et al.</i> [79]	Reduces pain when administered using an intravenous drip containing ketoprofen, sodium clodronate, glucosamine sulfate, and calcitonin

Joseph., <i>et al.</i> [57]	Higher vitamin C intake is associated with lower average cartilage T2, medial tibia T2 and medial tibia WOMBS (coeff_standardized range: -0.07 to -0.05, p<0.05)
Lafli Tunay., <i>et al.</i> [103]	Presurgical vitamin C administration led to reduced postoperative pain and total morphine consumption, and analgesic requirements
Li., <i>et al.</i> [81]	Ascorbic acid facilitates neural regeneration after nerve crush injury
Luo., <i>et al.</i> [105]	Vitamin C is potentially beneficial, and warrants consideration by orthopaedic surgeons in the treatment of a variety of musculoskeletal injuries
Naskar., <i>et al.</i> [82]	Treatment with vitamin C early on may reduce osteoarthritis severity
Okuba., <i>et al.</i> [83]	Topical applications containing vitamin C may reduce neuropathic pain
Oikonomidis., <i>et al.</i> [34]	Alleviation of oxidative stress with ascorbic acid may help to decelerate osteoarthritis disease progression
Park., <i>et al.</i> [4]	Intraarticular injections containing ascorbic acid protects osteoarthritic progression
Peregoy., <i>et al.</i> [24]	Vitamin C supplementation may be beneficial in preventing incident knee osteoarthritis
Riffel., <i>et al.</i> [84]	May contribute to anti-nociception in neuropathic pain states if combined with vitamin E
Ripani., <i>et al.</i> [85]	Vitamin C impacts inflammation favorably and benefits most people with early osteoarthritis
Saffarpour and Nasirinezhad [104]	Ascorbic acid produced a dose-dependent antinociceptive effect that seems to mediate through its interaction with N-methyl-D-aspartate receptors in a neuropathic pain model
Shapiro., <i>et al.</i> [86]	Ascorbic acid regulates multiple metabolic activities of cartilage cells
Shaik-Dasthagirraheb., <i>et al.</i> [87]	Vitamin C can serve as a free radical scavenger, and antioxidant, and is involved in the synthesis of several hormones
Tang., <i>et al.</i> [88]	Vitamin C reduces the oxidative stress and inflammatory response of muscles in the context of postoperative care
Wang., <i>et al.</i> [89]	Modifications of dietary antioxidant intake may be helpful for preventing hip osteoarthritis
Zollinger., <i>et al.</i> [36]	Reduces complex regional pain syndrome after wrist fracture

Table 1: Table Showing Possible Benefits of Attaining Optimal Daily Vitamin C Levels in Efforts to Ameliorate Osteoarthritis Pain Correlates.

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