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Review Article

Osteoarthritis and Vitamin C Pathogenic Insights and Therapeutic Potential

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Abstract

Osteoarthritis, the most prevalent musculoskeletal disease remains relatively impervious to a desired reversal of its progressive impact on mobility and life quality. Moreover, even if available, standard treatments may not be indicated, or efficacious, or safe and commonly fail to impact the disease directly. A disease with multiple progressively degenerating physical manifestations including joint tissue damage, inflammation, and muscle pathology, antioxidants such as vitamin C may prove helpful, especially in protecting vulnerable older adults from undue pain and suffering and excess joint destruction. Building on a prior in depth overview capturing almost all data on this topic as a 2019 search, here we present some newer data on this topic published since 2019 that furthers the view that vitamin C has noteworthy anabolic and catabolic properties that can be harnessed to mediate, moderate, or even prevent osteoarthritis joint damage in later life. Its vast protective and interactive attributes with joint and brain tissues show sufficient potential in the context of osteoarthritis pain and inflammation, as well as joint structure and cartilage physiology that is of paramount importance to validate and should be intently explored to prevent overlooking a promising non narcotic osteoarthritis pain and free radical reduction source.

Keywords: Aging; Ascorbic Acid; Cartilage; Intervention; Joint Inflammation; Osteoarthritis; Pain; Vitamin C

Introduction

Osteoarthritis a widespread highly disabling joint disease affecting many older adults and others has been and remains an immensely costly public health challenge with few means of its mitigation using safe cost effective approaches [1]. A commonly progressive disease that affects multiple joint tissues and their components as well as their physiology especially that of the cartilage tissue protective lining joints such as the knee, osteoarthritis is a chronic disease implicating a high presence of ROS (reactive oxygen species) known to degrade cell membranes, tissue biology and structure as well as other adverse pathophysiological mechanisms. As a result, as the disease progresses, the affected individual commonly experiences substantive bouts of pain, joint inflammation, muscle mass declines, joint stiffness, and multiple functional limitations with immense life implications for the sufferer, who is often an older adult, as well as their families, health providers, health economists, and health policy makers.

In this regard, another body of data has revealed vitamin C, also termed ascorbic acid, an essential highly potent water-soluble vitamin and micronutrient found of high health importance in general may have some bearing on understanding the emergence of osteoarthritis and its perpetuation and amelioration, due to its known tissue biology, growth, and developmental interactions including genetic and ROS interactions [2-4]. Studied widely for its promise in regard to trauma, pain and wound healing as well as cartilage regeneration its contribution to the structural support of joints, plus its additional ability to reduce fatigue and foster cognitive function

while attenuating harmful degrading oxidative processes associated with chronic diseases are fairly well established [5-8]. Other actions of note are its important neural modulation support functions such as limiting excessive small Aδ and C fiber sensory nerve activation that induces neuropathic type pain in the presence of suboptimal vitamin C, while playing a crucial role in collagen synthesis, stress control and immune functions, and thereby on health in general [5-8].

Applied in the realm of osteoarthritis more specifically [9] vitamin C appears of high relevance to efforts to minimize the magnitude and intensity of any prevailing joint destruction and pain that emerges over time due to its antioxidant properties that can potentially counter the production of damaging pain provoking free radicals that can potentially have multiple negative local joint as well as cognitive implications for the sufferer [8]. In contrast, its optimal presence and potential impact on wound healing processes and others may however help prevent associated or excess cartilage tissue damage, while fostering vitally important collagen synthesis and mental health status [8].

This possibility is important to explore because while several pharmacologic treatment approaches may well be temporarily helpful in the realm of osteoarthritis care and pain control, most fail to modify or reverse the disease process and its structural progression to any known degree and thus higher doses of medication may be needed over time. This is potentially problematic, for example in the older population where some members suffering from osteoarthritis may well be unable to tolerate these drugs for any long-term duration. In some cases the drug may prove toxic to joint tissues as well as collagen production, or have fatal side effects, for example if pain relief is dependent on narcotics. In addition to the expenses patients may have to incur, some recently tested biologically oriented therapeutic approaches have failed to show promise in slowing the rate of osteoarthritis joint space narrowing. Other data reveal some anti-inflammatory drugs can indeed hasten, rather than slow the disease process, and do not always reduce pain [10]. On the other hand, a strategy that can favorably influence the structural and functional properties of the cartilage lining of an affected joint, as well as its surrounding muscles and nerve supply, and bone in a positive way, while safeguarding or helping to foster overall physical and mental health, would be expected to be highly valuable in the context of pain relief or the prevention of excess pain, the symptom of most concern to osteoarthritis patients.

Aims

This review aimed to update the extent of support for the idea that vitamin C, an established mediator of tissue biology, growth, and development with powerful antioxidant and anti-inflammatory properties 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, genetic, molecular, and neurological processes, implicated in osteoarthritis, an idea disputed by several researchers, but not all.

Tested is the idea as to whether vitamin C presence has a distinct bearing on directing potential cartilage healing opportunities in osteoarthritis, as well as pain.

Methods

To achieve these abovementioned review aims, we elected to build on an extensive review of available documents housed in PUBMED, PubMed Central, and Google Scholar from 1990 up until 2019 using the key terms Vitamin C and Osteoarthritis/Muscle/Pain. More specifically, an updated overview of related research published between January 1 2019- June 10 2024 was sought.

To this end, all available 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 so the two systems are not strictly compatible. 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 only uses three data bases, these were taken to presumably house and capture the state of the art and gold standard papers on this topic sufficient for arriving at a reasoned opinion through a narrative lens. Readers can learn more by exploring the current cited reports as well as some prior reports Ballez., *et al.* [11], Grover., *et al.* [12] and Choi., *et al.* [13], Marks [14].

Results

As of June 1, 2024, the data bases examined revealed only a small number of relevant studies, for example, 4 in PUBMED 2024 and 2020, 12 in 2021, 10 in 2022, 7 in 2023. These data are clearly very limited in number and scope as far as what is needed to address prior gaps in this realm and arrive at firm conclusions, and especially when compared to other overriding themes dealing with osteoarthritis as well as vitamin C research over the same time periods. These data also render their take home messages very challenging to unify because the reports available stem largely from cross-sectional clinical research reports, review articles, or lab based studies on isolated tissues in animal models that may not replicate human osteoarthritis in the older person.

There is also no unifying underlying conceptual or theory base or consistent theme or terminology usage that can be extracted, and key words employed did not always yield research posted on the data base but not where anticipated. Indeed, even where modest numbers of articles were posted some focused on deficiency effects of vitamin C in osteoarthritis, some on its possible pain relieving or provoking supplementary effect, and some on its antioxidant or pro oxidant effect, its destructive effects or its failure to have any meaningful effect or opposing conclusions, for example Xu., *et al*. [15] noted vegetables intake that contains vitamin C to be helpful in averting knee osteoarthritis risk, but not at high levels.

Unfortunately, even if its cartilage-associated protective influence appears promising, once joint destruction has commenced, challenges arise in identifying precisely what works and why because sources and dosages or intakes of vitamin C discussed in lab studies, as well as some clinical studies and their comparability remains elusive at best as discussed recently by Frediani., *et al.* [16] Whether instruments and outcomes reported in current research reports are both reliable and valid is also hard to ascertain. For example is a vitamin C estimate that is dependent on memory or food recall and/or whether this includes or excludes supplement usage, quality and consistency of use, along with highly heterogeneous osteoarthritis clinical or tissue samples, and other design issues not problematic in its own right? Moreover, subjective measures of pain without verification must surely render the strength of any emergent relationships between vitamin C and osteoarthritis pain tentative at best even though at least two decades have been devoted to this topic in this and other related realms.

Since the resultant data do however show that vitamin C has important antioxidant properties against inflammation, as well as serving as a co-factor in for numerous biochemical reactions involved in the synthesis and assembly of cartilage collagen, and its matrix [14,17-19], it also has an affinity to exert chondroprotective and/or cartilage tissue regenerative effects [20-22], a universal agreement in this regard would undoubtedly prove of high significance. In particular, often used or administered alongside other interventions [23,24] and/or carefully studied in non clinical animal models of osteoarthritis joint damage [22] its singular effect on inflammation and other forms of pathology appears immensely noteworthy [25] as far as fostering chondrocyte proliferation and preventing articular damage [21]. As a result, several reports do suggest therefore that more should be done to determine if low vitamin C levels are pathogenic and if so, whether the presence of adequate dietary and/or supplementary levels of vitamin C or combination thereof is beneficial to an osteoarthritis sufferer [2,6,26,27] especially if muscle that houses vitamin C has already atrophied, along with structural features such as the surrounding joint ligaments, tendons, and bone quality and local and systemic inflammation prevails unabated [28-30]. It is duly observed as well that clinically relevant associations that can be harnessed quite readily are found to exist between vitamin C levels and chronic spinal pain, a common osteoarthritis complaint [31,32], and for selected cases suffering from osteoarthritis and requiring soft tissue and bone tissue enhancements it appears vitamin C has a strong bearing on the rate of post orthopedic surgical recovery processes [33,34].

Indeed, Chiu., *et al.* [35] argue that these aforementioned observations while not universally observed are worthy of exploration based on valid data showing vitamin C potentially reduces pain because its presence helps to decrease apoptotic cell death processes as well as the expression of pro-inflammatory cartilage chondrocyte derived cytokines and matrix metalloprotease degrading enzymes, even at low doses [21]. Another possible pain reducing mechanism involving vitamin C may implicate an initial reduction in the production of damaging chondrocyte enzyme activity, and thus less ROS-injury provoking chondrocyte and extracellular matrix breakdown [36]. Another is the prevention of oxidative injury as well as deterioration of associated musculoskeletal supportive and functional structures [11]. Another is improved chondrocyte viability and proliferation and possible regeneration [8,21,37].

The interesting finding that 100 percent of a group of end stage osteoarthritis sufferers undergoing knee replacement surgery had deficient vitamin C levels before surgery, and this remained true in 90 percent of cases after surgery tends to imply that the presence of an inadequate level of vitamin C intake may impact unfavorably on pain as well as inflammation resolution [28]. In contrast, adequate vitamin C plasma levels have been shown to have a favorable impact on pain [38-40], plus articular cartilage tissue viability, while possibly allowing for a decreasing analgesic need, and functional benefits. Indeed, a recent report shows drug delivery of vitamin C via bio active nano-magnetic particles in conjunction with a compound termed dexamethasone does tend to yield cartilage chondroprotective benefits that should be duly explored [41].

Discussion

Osteoarthritis, a highly disabling largely incurable joint disease and one where any form of palliative or reparative treatment and those that safely reduce pain, would be highly prized, remains largely dependent on an array of pharmacologic and/or surgical interventions of varying degrees of efficacy and effectiveness [42,43]. 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 has been forthcoming in the realm of applying vitamin C associated research towards understanding osteoarthritis pain and its possible reduction or prevention in the older adult population specifically, despite several well-founded reasons for considering this possibility.

That is, despite a reasonably strong underlying rationale for believing that vitamin C is tentatively important for purposes of ensuring optimal joint health, and that older 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 poorly studied, when compared to other topic areas concerning osteoarthritis pathogenesis and mitigation. Reflecting a patchwork of interesting studies but with no seemingly consistent underlying hypothesis, certain parameters that may not have been considered [2], plus widely diverse modes of inquiry and design no conclusions can be drawn with any degree of certainty. Indeed, as in the past, current data continue to be largely suggestive rather than definitive despite advances in identifying and studying cellular and molecular levels of vitamin C and cartilage cellular impacts [44] and findings of an associated injury related ability to foster muscle regeneration [45].

This seems unfortunate because some promise has been forthcoming wherein several authors have noted a potentially valuable role for considering how vitamin C might mediate or moderate the highly resistant form of pain experienced by people with osteoarthritis, and its impact on function and life quality, including related bone damage when examined in the clinical or applied realm [13,46-50]. Moreover, multiple preclinical studies strongly support the possibility of vitamin C as an adjunct for alleviating, minimizing, ameliorating, or reversing osteoarthritis cartilage damage. Vitamin C also possesses multiple additional capacities for prevention of osteoarthritis progress, including decreases in cell death and the expression of damaging pro-inflammatory cytokines, in addition to its well documented key antioxidant actions [11].

However, despite some favorable clinically applicable findings in recent years, most current researchers are calling for more carefully designed efforts to address documented design shortcomings in promising studies and to thereby foster the ability to resolve the presently divergent viewpoints concerning its efficacy as well as safety of vitamin C, as this pertains to osteoarthritis pathology and pain amelioration, where no firm conclusions prevail as of mid 2024. As in other realms of clinical research as well as preclinical explorative efforts, prospective well controlled research designs are imperative along with insightful research questions and methods of answering these current uncertainties more objectively using well defined and stringent measures, such as plasma level vitamin C assays plus pain measured at regular intervals. Studies designed to identify how older subgroups with vitamin C deficiencies may or may not respond to supplementary forms of vitamin C, rather than failing to do this is also strongly indicated as this group will likely be vulnerable to ROS injury and a high oxidative presence. Careful attention to assessing dose concentration relationships between vitamin C supplements, with and without any dietary sources, medications that may impede vitamin C anabolic processes, and pain as well as functional correlates of various osteoarthritis cases in the clinic can also help ensure that clinically meaningful relationships that emerge are robust and can be demonstrated based on validated instrumentation and reproducible methods and statistical procedures.

In the interim, what we do know is that vitamin C is clearly an essential co-factor for fostering normal collagen synthesis, including collagen X [51], a major structural element of articular cartilage, and its surrounding tissues [52], as well as for other vital physiological chondrocyte, and bone cell functions [53]. It also appears deficient vitamin C levels are associated with pain provoking inflammation that often accompanies osteoarthritis [54]. There are also vitamin C transporter deficiencies that have the potential to markedly impact cartilage cell metabolism as well as cartilage collagen production, matrix formation and assembly, significantly and adversely that could explain osteoarthritis pain modulation challenges to some degree [55]. Vitamin C presence does however appear to be accompanied by improved pain scores, while helping subjects achieve better functional outcome than not [49]. As well, surgery for osteoarthritis or joint injuries may be optimized by carefully applied vitamin C supplements [34].

It is also possible that although Joseph., *et al.* [48] discount any vitamin C impact on osteoarthritis, its efficacy as an osteoarthritis protective factors has not been revealed uniformly and examined meticulously and comprehensively so as to rule out competing factors. Although often discussed, the role of suboptimal or noxious vitamin C supplementary doses, potentially unreliable assessments, omitted assessments, and the statistical problems of applying aggregated data from limited albeit diverse samples as recorded retrospectively or on a single occasion remains. It is possible too that more attention to the notion that implies the presence of a persistent vitamin C deficiency is a potentially debilitating health factor that may inadvertently raise the risk for osteoarthritis joint damage, while retarding its recovery potential, which is poorly studied, should be considered of high import to examine. In addition, it is acknowledged such data may exist but may have been omitted inadvertently.

However, after surveying more than 150 related papers in 2018 [14] and another 50 since then in this report, wherein most were located in the world's leading data base of PUBMED-deemed reliable and peer reviewed- it appears safe to propose that persistent vitamin C deficits appear to have the potential to accelerate or magnify any prevailing joint pain found in most older adults suffering from osteoarthritis. It may also be that an individual struggling with painful osteoarthritis who is under stress is particularly vulnerable, and has an increasing need for long-term vitamin C supplementation to minimize health challenges that provoke ROS-injury [50], even if refuted [49].

In sum, there appears to be a valid need to generate more insight into how vitamin C may be an important osteoarthritis pain correlate, and to permit more adequate translation of prevailing lab data to the clinic. In particular, research attempts designed to differentiate the association of vitamin C levels among distinctive osteoarthritis sub-groups with and without verifiable oxidative damage may prove insightful. After that, meticulously and rigorously designed studies to rule out competing hypotheses, and to avoid undesirable cross sectional inferences that do not take into account the fact that reported vitamin C intake on a food survey delivered retrospectively may not be the same as actual time based plasma levels, and that its effects may be both disease specific, as well as dose-dependent and take weeks or months to unfold and be influenced by gender among other factors such as age and health and disease status [54]. The efficacy of tailoring doses for reducing osteoarthritis pain and moderating its development as well as its adjunctive role in mediating pain should also be examined and remain open until more artificial intelligent data that can do this meaningfully prevail.

Conclusion

In accord with past research efforts, 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 or absence of optimal levels of vitamin C, even if not favorably viewed in this regard all instances.

However, the role and possible impact of varying vitamin C levels on osteoarthritic pain remains to be proven more substantively, including the differential impact of various forms of application and dosages and their longitudinal influence on diverse joint structures, biomarkers of pain, as well as function using advanced technology. Methods of vitamin C delivery that need to be studied in older adults with osteoarthritis of different degrees in their own right are-

- Oral supplements of varying dosages, combinations, formulae, and usage instructions
- Intra-articular injections or delivery
- Iontophoresis using continuous electric current
- Beverage supplements
- Dietary fruit, vegetable and herbal sources
- Freeze-dried dietary powders
- Freeze-dried beverages
- Laser facilitated trans dermal delivery

In this regard, even if this aforementioned suggestions require considerable time, funding, and dedication, chemically identified as ascorbic acid, vitamin C clearly has the potential to play a potentially salient role in preventing excess osteoarthritis tissue destruction and repairing this or at a minimum offering some degree of pain mitigation all things considered.

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 fostering cartilage tissue protection and with this a more positive outlook rather than a negative painful and disabling array of harmful osteoarthritis consequences.

Benefits other than pain including cartilage repair, bone maintenance, muscle function, collagen production, stress reduction, neural regeneration, mitigation of osteoarthritis severity and progression, enhanced free radical scavenging, and antioxidant processes and their underlying mechanisms of action should be duly sought as well with the expectation that many older adults will suffer less, and place fewer demands on health providers and budgets.

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Conflicts of Interest

None.

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