Novel Techniques in Arthritis & Bone Research
ISSN: 2575-8888

Juniper Publishers
key to the Researchers

Mini Review
Volume 2 Issue 5 - May 2018
DOI: 10.19080/NTAB.2018.02.555600

Nov Tech Arthritis Bone Res

Vitamin C and Articular Integrity

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Submission: May 09, 2018; **Published:** May 15, 2018

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Abstract

Osteoarthritis, a debilitating disease predominantly affects articular cartilage. Many attempts to understand the pathogenesis and best method of protecting articular cartilage from degeneration have proved non-conclusive, however. Vitamin C or ascorbic acid, an antioxidant with many regulatory functions can play a role in both disease onset and its prevention, but this fact has not proved to be strongly associated with either the osteoarthritis disease pathology or its prevention or retardation. This article discusses some of the diverse findings in the available research and offers some directives for future research and practice.

Keywords: Articular cartilage; Ascorbic acid; Collagen; Osteoarthritis; Vitamin C

Introduction

Vitamin C, more recently termed ascorbic acid, is an extensively studied highly potent water-soluble vitamin and mediator of tissue biology, and wound healing, among other functions. Examined in the context of several diseases attributable to oxidative degenerative processes such as atherosclerosis, and in a number of in vitro experiments, vitamin C is relatively under-represented in our view as a possible osteoarthritis mediator or moderator in clinical contexts. Moreover, the diverse studies that do exist while mostly supportive of a possible protective or pathogenic role for vitamin C in the osteoarthritis pathological cycle, no agreement as to whether vitamin C can allay, retard, or moderate the disease process, currently deemed to predominantly impact articular cartilage irreversibly.

Aims

To examine what do we know in this regard, and what consensus if any can be reached.

Methods

All relevant data located in Pub Med from 1980 - May 1, 2018 using the key terms Vitamin C and Articular Cartilage or Ascorbic Acid and Articular Cartilage-the tissue deemed key in the osteoarthritis disease process were reviewed for their relevance.

Results

After downloading and reading all pertinent articles, the data revealed that although nutrient levels in general were long disputed as having any clinically salient role in the osteoarthritis disease process, they are now known to have the potential to influence both the development and the progression of osteoarthritis, presumably by their ability to modulate or mediate, articular cartilage matrix biosynthesis and degradation processes. In this context, there is some evidence that cartilage matrix synthesis may specifically be affected positively in the presence of certain ascorbic acid or vitamin C levels. This is attributed to the properties of vitamin C as an antioxidant and co-factor for numerous biochemical reactions, especially the synthesis and assembly of cartilage collagen [1], aggrecan synthesis [2], and post-translational modifications of collagen [3].

Blackburn et al. [3] who studied the expression of the sodium-dependent vitamin C transporter 2 system, the only known sodium coupled vitamin C transporter isoform present in articular cartilage, found that the expression of this transporter was significantly altered in human osteoarthritic tissues. This finding, along with data showing vitamin C deficiencies inhibit collagen synthesis [4], suggested the modulation of this transporter mechanism might be an important factor that could influence the development of osteoarthritis. Its viability might hence be responsible for tipping the state of balance between cartilage degradative processes versus cartilage repair or maintenance processes.

Malicev et al. [5] however, found-vitamin C to induce apoptosis in a cell culture of chondrocytes after 18 hours of of

cultivation, which was dose dependent and significantly affected by the presence of serum. The increased number of vitamin C induced apoptotic cells was associated with DNA fragmentation and morphological changes of the cells. Gallagher et al. [6] also reported no evidence in the literature to support or refute their use for chondroprotection. Earlier however, Kraus et al [7] showed ascorbic acid increased rather than decreased the severity of spontaneous osteoarthritis in animals as discussed by Sharma et al. [8], and Chaganti et al. [9] found higher serum vitamin C levels in cases of knee osteoarthritis with more rapid disease progression.

Yet, Hahn et al. [10] concluded that the use of additive compounds such as ascorbic acid reduces cryoprotectant toxicity in articular cartilage and may help improve cell recovery after cryopreservation. This group studied injectable hydrogels loaded with ascorbic acid and found these may be helpful for accelerating cartilage regeneration as proposed by Rampichova et al. [11]. In addition, cases with knee osteoarthritis, which are sometimes prescribed intra-articular injections of glucocorticoids, such as triamcinolone acetonide, were found to benefit from the addition of vitamin C. This finding is supported by evidence that vitamin C can decrease oxidative stress and increase cartilage viability, while attenuating the toxicity of these injections [12] as well as the progression of osteoarthritis in an animal model [3].

In addition, Chiu et al. [13] reported vitamin C has the capacity to decrease apoptotic processes and the expression of pro-inflammatory cartilage chondrocytes cytokines and matrix metalloproteases, while providing its well-known ant oxidation effects. Not surprisingly, Chang et al. [14] similarly found vitamin C efficiently protected human chondrocytes against damage induced by this chemical. That is, as observed by Chiu et al. [13], Chang et al. [14] found the administration of vitamin C protected their cultured chondrocytes from apoptosis, while it also increased senescence and loss of viability of the chemically induced oxidative stressor. It also appeared to stimulate proteoglycan and collagen expression, and inhibited chondrocyte differentiation that usually occurs in the presence of oxidative stress. De Arruda et al. [4] too reported that efforts to foster the uptake of a form of vitamin C (L-ascorbic acid) using iontophoresis produced measurable improvements in the thickness of the calcified and non-calcified cartilage tissues in their model.

Ibold et al. [15] who evaluated and compared the effect of different ascorbate forms and concentrations on in vitro cartilage formation in porcine chondrocyte high-density pellet cultures for over 16 days found all supplementations caused a similar effect except for low concentration of ascorbic acid, which resulted in an even higher expression level of all marker genes. This suggests that low doses of ascorbate are extremely effective compared to higher dose concentrations. An in vitro study by Sharma et al. [8] further showed that vitamin C supplementation of chondrocytes after static loading reduced the normal degenerative processes of these cells caused by static loading, thereby improving the cellular health and functioning of articular cartilage. Likewise, Koike et al. [16] found a vitamin C derivative to effectively suppress mitochondrial superoxide generation and delayed cartilage degeneration in a mechanical overload model, and which appears to be of considerable utility.

Earlier, Kim et al. [17] found that ascorbic acid stimulated the proliferation of chondrocytes and helped to maintain the chondrogenic properties of the cells in an alginate beads culture. In contrast, deficient levels of vitamin C have been found to decrease collagen synthesis in articular cartilage, tendon, and muscle, plus bone density, all possible structural changes that could heighten the risk for osteoarthritis pathology, as well as joint injury [18]. By contrast, since optimal levels of ascorbic acid could help maintain optimal collagen synthesis [2], Wang et al. [19] suggests a beneficial effect of fruit consumption and vitamin C intake as they are associated with a reduction in bone size and the number of bone marrow lesions, both of which are important in the pathogenesis of knee osteoarthritis. While they stated their findings need to be confirmed by longitudinal studies, they highlight the potential of the diet to modify the risk of osteoarthritis.

Conclusion

Despite some arguments and evidence to the contrary, more weight rather than less weight seems to support the potential benefit of continuing to examine the role vitamin C might play in the onset and progression of osteoarthritis. Although this could reflect publication bias, since the many current reviews of articular cartilage and what contributes to its integrity or dissolution have been inconclusive, and most have failed to examine a role for vitamin C despite 30 years of robust preclinical endeavors, more basic research to tease out any possible clinically meaningful role for vitamin C in impacting articular cartilage and the surrounding joint tissues implicated in osteoarthritis is warranted in our view and would appear to be beneficial. In particular, it is hard to refute that there is a strong rationale for deficient vitamin C levels in the osteoarthritis pathology process, given that this substrate is essential for normal collagen synthesis, including collagen X [20,21], a major structural element of articular cartilage, and its surrounding tissues [22], while revealing a capacity for regulating the energy status of maturing chondrocytes, plus related alkaline phosphatase activity [20]. It is also a powerful antioxidant [2], and involved in wound healing processes and others such as the synthesis of several osteoblast-related proteins [21]. Moreover, in addition to nutritional vitamin C deficiencies, and age associated declines in vitamin C levels that may accelerate oxidative damage in cartilage tissue [23], abnormalities in the vitamin C transporter mechanism in cartilage may be implicated in osteoarthritis, as

How to cite this article: Ray Marks. Vitamin C and Articular Integrity. Nov Tech Arthritis Bone Res. 2018; 2(5): 555600. DOI: 10.19080/NTAB.2018.02.555600

may similar deficiencies in the surrounding muscle, tendon and bone structures, and the presence of inflammation that often accompanies the disease may rapidly deplete available levels of vitamin C [24]. Clinical manifestations of vitamin C deficiency paralleling those in osteoarthritis are fatigue, joint swelling, muscle aches and pains, and emotional changes [25], that should not be discounted. Conversely, coupled with appropriate doses of targeted mechanical stimulation, vitamin C may assist in improving the mechanical properties of regenerating articular cartilage [26].

Consequently, subject to further study, and as outlined by Kurz et al. [27], a diet supplemented with vitamin C might be important in the prevention of mechanically-induced osteoarthritis, as may other forms of delivering vitamin C [16]. Administering vitamin C and ensuring its entry into the cartilage tissue, for example through nanotechnological approaches or injection of a safe vitamin-C permeable derivative [11,16,28], may similarly help to foster cell differentiation and the development of chondrogenic cells [11], and improve cartilage quality and thickness [4], while reducing the risk of cartilage loss and osteoarthritis and its progression [13]. The addition of vitamin C and its co-administration with conventional drugs [29,30] might also increase the viability of cartilage exposed to toxic levels of glucocorticoids-often used to treat inflammatory recalcitrant cases [12] or as a secondary therapeutic agent to reduce oxidative damage and deterioration of the involved osteoarthritis tissues [29]. The use of L-ascorbic acid and other vitamin C analogues to repair articular cartilage defects also holds a lot of promise and should be explored further [31]. We thus concur with Hart et al. [32] that the role of vitamin C in preventing osteoarthritis has tremendous potential, though results in animal and human studies are controversial, heterogeneous, and show few human-based cross-sectional studies or prospective trials. Other possible benefits are shown in Table 1 [33-40].

Table 1: Selected Potential Benefits of Vitamin C in Reducing Cartilage Degeneration.

Research Group	Key Findings
Aghajanian et al. [33]	Exerts a positive effect on trabecular bone formation and is an important regulator of chondrocyte fate differentiation
Burger et al. [34]	Helps to expand subchondral bone osteoblasts in vitro while maintaining their special cellular characteristics.
D'Aniello et al. [35]	Regulates extracellular matrix/collagen homeostasis + plays key role in differentiation of mesenchymal stem cells
Huang et al. [36]	Modulates and enhances the anti-catabolic effect of hyaluronic acid
Phull et al. [37]	Fucoidan + vitamin C reduces oxidative stress, edema and arthritis-mediated inflammation
Kraus et al. [7]	Stimulates mRNA and protein expression
Sangi et al. [38]	Low vitamin C intake is a possible risk factor for knee osteoarthritis
Sato et al. [39]	Suppresses matrix metalloprotease gene expression in scaffold free cartilage like sheets
Schwartz and Adamy [40]	Fosters biosynthesis and distribution of cell layer and medium fractions of newly synthesized proteoglycans-in both normal and osteoarthritic chondrocytes

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