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Research Article

Vitamin D and Cartilage: Does Vitamin D Influence Cartilage Integrity?

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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 work aimed to examine: 1) whether vitamin D, a powerful steroidal hormone involved in many physiological processes is an important determinant of osteoarthritis pathology, and 2) whether vitamin D supplementation can potentially restore articular cartilage integrity in damaged joints. To this end, a comprehensive overview of relevant English language research reports published over the last 30 years was undertaken. Regardless of study design, these data revealed no clear conclusion with respect to either study question, a wide array of study substrates, approaches, and outcome measures, plus equivocal findings even when similar research designs were applied, along with similar samples. In light of the limited consensus reached when examining the present data base, plus the presence of substantive methodological concerns within this literature, it is concluded more research to carefully delineate the possible protective, reparative or aversive role of vitamin D in mediating articular cartilage status in more representative samples is warranted, and will potentially prove of immense clinical value.

Keywords: Articular cartilage; Bone, Muscle; Osteoarthritis; Prevention; Vitamin D

Background

Osteoarthritis, a chronic health condition resulting in immense pain and disability is strongly associated with progressive lesions of the articular cartilage tissue lining synovial joints such as the hip and knee. Often considered an inevitable component of aging with no effective means of prevention or treatment, discussions about whether vitamin D, a key mediator of bone and cartilage tissue metabolism [1] is of potential value for reducing the risk of acquiring this disease, and its subsequent disabling symptoms have ensued for some time with no conclusion.

Given the enormity and extent of the disability incurred worldwide by adults in their older years who are diagnosed with osteoarthritis, and some evidence that a vitamin D deficiency may be implicated as one possible factor promoting the disease onset, and its progression, it was believed a comprehensive updated review of this line of inquiry would prove both timely and insightful. To this end, this brief examines whether there is a consistent directional association between vitamin D levels and the presence or absence of osteoarthritis in older adults. It further examines what is known about the direct effects of vitamin D on articular cartilage explants or models of arthritis conducted in the laboratory. Both basic research studies concerning vitamin D and its impact on healthy and damaged cartilage tissues and cells, plus related clinical studies were examined to ascertain whether there is conclusive evidence in favor of a possible role for vitamin D in the overall pathologic process of osteoarthritis and its possible treatment.

The scientific rationale for pursuing this line of thought is that a considerable volume of evidence does indicate that vitamin D or cholecalciferol, a collective of structurally related metabolites obtained either from dietary sources, dietary supplementation, and/or sunlight, is of potential relevance in the context of the pathogenesis of osteoarthritis, given its role in development, growth, and maintenance of a healthy skeleton. In addition, since cells such as chondrocytes of articular cartilage, the tissue most consistently identified as problematic in this disorder, possess vitamin D nuclear receptors [VDR (nuc)] as well as cell surface vitamin D receptors that regulate gene transcription [2,3], it is possible that these receptors, as well as the presence of vitamin D interact to impact chondrocyte gene expression and the biological responses of these cartilage cells. Vitamin D can also affect joint status indirectly through it regulatory impact on muscle and/or bone [5-9]. In addition, since inflammation [10], often accompanying osteoarthritis damage, and factors such as obesity [11], impaired neuromuscular function and balance [12] depression [13] and pain [14], implicated in osteoarthritis, can all be influenced by the prevailing degree of vitamin D, it appears that the presence of any vitamin D deficiency would do more harm than good in terms of directly or indirectly promoting optimal cartilage viability and joint integrity as outlined in (Figure 1).

To better understand the extent to which vitamin D is clinically relevant in the context of osteoarthritis prevention and treatment this present review examined the degree of consensus in support of a role for vitamin D in predicting or influencing the extent or rate of cartilage synthesis and/or degradation, either directly or indirectly.

Since the literature remains divided as to whether supplementation may be desirable for promoting osteoarthritic cartilage healing, or

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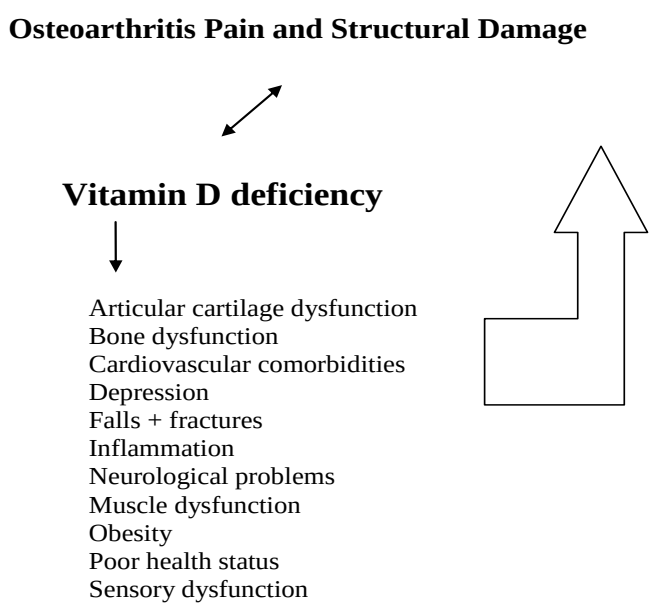

Figure 1: Potential link between the impact of vitamin D deficiency and osteoarthritis.

for preventive purposes, it was felt a broad updated examination of all the available literature on this topic might be helpful. The terminology adopted in this paper to describe vitamin D was that applied in the related literature, rather than any generic term, there being considerable diversity in this respect, and a general lack of any standardized approach.

Methods

Using the search terms Vitamin D and Articular Cartilage, accepted sources of information including literature reviews, case studies, cross-sectional studies, prospective studies, and topics related to cartilage metabolism and the topic of vitamin D were sought. In this respect PubMed had 77 articles dating back to 1963, with 14 being published in the last 5 years. Scopus had 110 and Web of Science 159 since 1959, only 19 though were clinically oriented. Using the key words Vitamin D and Osteoarthritis in the Web of Science with all data bases combined yielded 734 articles. To identify key issues in this diverse literature, the downloaded papers were fully read and divided into those that were derived from basic research studies, versus those that were performed clinically. A narrative perspective was adopted, since very diverse topics and samples or substrates were used, vitamin D levels and measurement methods employed were inconsistent, and study duration, design, and outcome procedures were non uniform.

Results

In vitro studies

Among the diverse array of studies that have attempted to examine linkages between the application of vitamin D in its bioactive form 1,25 (OH2) D3 and articular cartilage physiology and structure, Chen et al. [15] who used rat cultured chondrosarcoma chondrocytes as a substrate, observed that the vitamin D compound activated metalloproteinase 3 expression in a dose and time dependent manner, and inhibited type II collagen and aggrecan expression. This finding is intriguing because an increase in this specific enzymatic expression and a decrease in aggrecan expression would be potentially harmful to the articular tissue. Hence, contrary to playing a therapeutic role, this research implied vitamin D can activate harmful enzyme expression in rat chondrosarcoma chondrocytes, which is thought to represent possible responses in the human condition. While this detrimental cycle of events may occur in the context of human osteoarthritis, or if the optimally recommended vitamin D dosage is exceeded, perhaps, the substrate examined was not sufficiently representative of the responses of an actual osteoarthritic chondrocyte, and the non physiological vitamin D concentrations examined resulted in the observed trend towards destructive rather than reparative processes.

These aforementioned results, which should not be ignored, do not however comport with those of others. Shen et al. [16], for example, who approached their examination of the role of 1,25-dihydroxyvitamin D [1,25(OH)2D] or vitamin D deficiency in the context of temporomandibular osteoarthritis using a mouse model, showed bone mineral density and subchondral bone volume were reduced in the context of any deficiency of this vitamin in the mandibular condyles. In addition, the joint surfaces were found to have collapsed, and cartilage was thinner, implying a vitamin D deficiency can produce an erosive type of osteoarthritis.

In further support of a role for vitamin D on the functional properties of chondrocytes, Hdud and Loughna [17] found that rather than becoming uniform in nature, equine articular chondrocytes exposed to the active form of vitamin D did not undergo the de-differentation process normally observed in these cells. Hence, this study supported a protective effect of 1 vitamin D in the form of alpha, 25-dihydroxyvitamin D3 on articular cartilage cells in this equine model. This result is also consistent with that of Li et al. [18] who used a rat model, and where a vitamin D deficient diet aggravated cartilage erosion, while vitamin D supplementation yielded a protective effect in the ovariectomy-induced form of osteoarthritis. This was a well-designed study with 7 groups including a sham group comparison.

In addition, when using the rat as an experimental model, Pascual-Garrido et al. [19] concluded that there is a negative impact on cartilage when low levels of vitamin D prevail. In partial support of this aforementioned finding, a study by Castillo et al. [20] who also employed a rat model of osteoarthritis, did find vitamin D supplementation to have a protective effect at the outset of the disease, but not at the later chronic disease stages.

Sugiyama et al. [21] who examined the effects of vitamin D in the form of 25-hydroxy-cholecalciferol on the disease entity known as osteochondrosis in a swine model, noted vitamin D supplementation generally fostered a series of normal endochondral ossification processes, while inhibiting progression of osteochondrosis. It was suggested that the vitamin D supplementation helped to regenerate cartilage tissue that had been destroyed. Similarly, in a study that utilized both a mouse Lyme arthritis and collagen-induced arthritis approach, it was further observed that vitamin D supplementation along with an adequate diet inhibited the progression of the Lyme form of arthritis. The symptoms of the mice with early stage collagen-induced arthritis were also reduced compared to those of untreated controls if Vitamin D or its analog was added to the diet [22].

In sum, among the small array of diverse studies examining the association between vitamin D and articular cartilage in various target

Table 1: Sample of key clinical investigations conducted over the last 25 years in efforts to examine linkages between vitamin D and osteoarthritis (OA) showing variability in samples, joints examined, approaches, and findings.

Authors	Study design	Sample	Finding
Bassioni et al. [49]	Prospective	38 subjects with and without knee OA observed over 12 month period	25(OH) D levels were significantly decreased in the subjects with knee OA Medial meniscal deterioration was seen in patients with low vitamin D levels Vitamin D deficiency may play a role in the progression of medial compartment knee OA
Chaganti et al. [29]	Cross sectional	1104 elderly men with hip OA	Men with vitamin D deficiencies are at high risk for hip OA Vitamin D therapy is warranted for augmenting health in the elderly
Felson et al. [43]	Examined 25(OH)D levels in subjects longitudinally	There were 715 subjects in one study and 277 from another who were for vitamin D levels and radiographic worsening, but most knees had no evidence of OA at baseline	Vitamin D status was unrelated to the risk of joint space narrowing or loss of knee joint cartilage
Goula et al. [25]	Prospective	164 patients with knee or hip OA	A large percentage of patients were vitamin D deficient (81.7%); 15.2% were vitamin D insufficient, only 3% were vitamin D sufficient
Grazio et al. [36]	120 patients with psoriasis, rheumatoid and osteoarthritis had serum vitamin D levels analyzed	In OA cases, 97% subjects had serum vitamin D deficiencies	Prophylactic supplementation with vitamin D is recommended for these patients
Hussain et al. [24]	Prospective	9135 adults older than 40 undergoing hip arthroplasty for OA	Increasing serum 25-hydroxyvitamin D levels were associated with hip arthroplasty increased risk in males
Jansen et al.	Cross sectional	Examined elderly cases with advanced knee OA awaiting surgery	A high prevalence of vitamin D deficiencies was evident
Jin et al. [23]	In a 2 year randomized controlled trial, 209 subjects received monthly oral vitamin D treatments; 204 with knee OA did not	There were 413 completers of the study, all with initial low 25-hydroxyvitamin D levels, who had symptomatic knee OA	Monthly treatment with oral vitamin D (50,000units) does not produce significant clinical or cartilage volume structural differences in vitamin D deficient knee OA cases over time Results do not support vitamin D supplementation to prevent pain or cartilage loss
Malas et al. [26]	Investigated the association between vitamin D levels and distal femoral cartilage thickness in healthy subjects	80 patients classified into 3 subgroups according to vitamin D levels were examined	The severe deficiency group had thinner femoral cartilage thickness, and it was concluded low vitamin D levels affect femoral cartilage thickness negatively
McAlindon et al. [44]	Prospective	146 cases with knee OA	There was a 4% cartilage loss in the experimental as well as the control group
Muraki et al. [46]	Cross sectional	787 knee OA cases in the United Kingdom, mean age 65.6 years	Vitamin D may be more strongly associated with pain measured on a questionnaire than radiographic change according to a general estimating equation
Yoshimura et al. [35]	Prospective	1384 cases with osteoporosis or OA were followed for 3 years	Higher serum 25D levels do not prevent knee OA or lumbar spondylosis based on survey responses
Zhang et al. [30]	Prospective	418 knee OA patients	Approximately 16% sample had low vitamin D levels. Between baseline and follow-up 15% progressed in joint space narrowing scores. deficient in vitamin D have an increased risk of knee OA progression compared with those with greater vitamin D serum concentrations

models of osteoarthritis, most imply some relationship exists between vitamin D and cartilage integrity. The direction or magnitude of this effect is not consistent though, and while vitamin D may be deemed beneficial in some instances, in others it may prove more deleterious than not and facilitate cartilage erosion [15]. With no definitive model, or study approach, the observed outcomes may depend on the substrate employed, the degree of cell dysfunction present, the measurement approaches employed, and durations of exposure among other factors.

Clinical studies

Among the available clinical studies that have examined the nature of vitamin D and osteoarthritis pathology in some way, meta-analyses to establish what is known about relationship do not necessarily concur. As well, both positive and negative conclusions prevail when examining similar research questions, rendering these data difficult to collate collectively (Table 1).

For example, while some analyses imply vitamin D is ineffective for treating knee osteoarthritis [23], and can increase the risk of hip arthroplasty [24], others imply a high percentage of patients with hip or knee osteoarthritis are vitamin D deficient, even if they live in sunny climates [25], and that a vitamin D deficiency has an adverse impact on femoral cartilage thickness [26]. Yet others failed to support a link between vitamin D and the progression of osteoarthritis as outlined by Gallagher et al. [27], and Konstai et al. [28]. By contrast, other data have shown men with hip osteoarthritis to be deficient in vitamin D [29], and to have an increased rate of progression of knee osteoarthritis [30]. As well, Bergink et al. [31] who analyzed knee osteoarthritis sub groups found there were significant associations between low vitamin D levels and prevalent joint space narrowing as well as progression of the disease, which concurs with McAlindon et al. [32] who found a low intake along with a low serum level of vitamin D can increase the risk of developing knee osteoarthritis. Although association does not prove causation, the low serum levels of vitamin D also predicted loss of cartilage, as assessed by loss of joint space and osteophyte growth.

Ding et al. [33] too found sunlight exposure and serum 25(OH) D levels of vitamin D and the extent of knee cartilage loss as assessed by radiograph or magnetic resonance imaging were associated. In particular, since this group employed the whole range of vitamin D levels, rather than using any predefined cut-off points, they were able to conclude that achieving vitamin D sufficiency may prevent and/or retard cartilage loss in knee osteoarthritis. This conclusion was recently supported by Mabey et al. [34] as well as Maaty et al. [6], while again refuted by Yoshimura et al [35] who found no link between vitamin D and knee osteoarthritis.

However, the list of competing conclusions continues with findings by Grazio et al. [36] who compared vitamin D serum levels among differing rheumatic disease patients, in the face of fairly strong evidence for a number of mechanisms that can explain how osteoarthritis and deficient vitamin D levels are linked [37]. These include, but are not limited to reports that vitamin D may play an important role in osteoarthritis by way of bone mineralization and cell differentiation, pain sensitization [14], muscle strength [5,38], inflammation [39], and high obesity levels and worse function, which are risk factors for osteoarthritis. Vitamin D is also likely to benefit efforts to prevent falls that lead to joint injury [40], reduce the risk of depression [41] that can lead to physical activity declines and an increased risk of joint attrition (Figure 1). Lazlett et al. [42] who conducted a prospective five year study concluded that a moderate vitamin D deficiency independently predicts incident, or worsening of, knee pain over 5 years and, possibly, hip pain over 2.4 years.

In sum, several researchers imply there is no added value of recommending vitamin D supplementation in the context of osteoarthritis pathology, and that such an approach may even do more harm than good. Yet, this conclusion is far from universal, and a reasonable body of evidence suggests the contrary. With a strong rationale for hypothesizing a moderating or mediating association between vitamin D and osteoarthritis joint damage, it appears further research in this area is indicated.

Discussion

Osteoarthritis, the most prevalent form of arthritis is a major cause of disability among older adults. Predominantly affecting the articular cartilage tissue lining the freely moving joint, articular cartilage is a prime target of strategies to prevent, reverse, or ameliorate osteoarthritis disability and pain. To this end, it has been argued that vitamin D, a steroid hormone involved in fostering functions related to the musculoskeletal system, may be implicated in the osteoarthritis pain cycle [34]. This brief sought to examine the strength of this hypothesis given that the utility of vitamin D in the context of osteoarthritis disease progression has been disputed [23,35,43-45], but in other cases outlined in Table 1-a reasonably strong positive relationship consistent with results of the most *in vitro* basic studies on the importance of vitamin D in influencing musculoskeletal health and disease prevails. Reasons for the diverse conclusions may stem partially from the diverse methods used to examine the relationships in question, the different stages of the disease and joints studied, the modes and duration of exposure of vitamin D usage in intervention studies, the failure to employ effective controls to ensure vitamin D is the active ingredient in intervention studies, plus dissimilar quantitative measures and research questions [34]. In larger studies, the presence of measurement error, uncontrolled sources of error, insensitive outcome variables, and short study durations may explain some of the conflicting results.

In addition, even if some of the study designs of negative results can be considered rigorous, there appears to be a disconnect between results of these studies and studies that show vitamin D is able to favorably influence bone and muscle health, as well as articular cartilage status, and possibly pain [46]. Moreover, the ability of vitamin D to slow or prevent the disease which appears quite limited and non-conclusive, may reflect the lack of adequate follow-up, the failure to employ sophisticated biochemical, biopsy, and biomechanical outcome measures, the stage of the disease examined, and the nature of the applied vitamin D assay and supplement-where used, among other factors.

On the other hand, given the fact there are existing studies to the contrary, as well as numerous methodological challenges in the related research as listed above, it does not seem possible to support the conclusions of Gallagher et al. [27] that vitamin D has no chondroprotective effect. This is because more basic studies than not imply vitamin D can serve a protective function or prevent excessive erosion of cartilage. Moreover, low intake of vitamin D is a possible risk factor for knee osteoarthritis, especially in women [47], and people diagnosed with osteoarthritis and low serum levels of vitamin D do show increased rates of disease progression according to Loeser et al. [4], and possibly more inflammation and obesity [11]. The observed role of vitamin D nuclear receptors and their impact on gene function in cells such as chondrocytes, and clinical observations that there is a link between vitamin D deficiency and life quality in older knee osteoarthritis cases [48] does in our view strongly imply more research in this realm is not only warranted, but might prove highly fruitful for advancing our understanding the disease itself, as well as its amelioration potential.

It is also possible that further research will reveal that osteoarthritis exacerbates the availability of vitamin D due to its curtailing impact on outdoor activity, and the low levels of vitamin D that ensue promote more progression of the cartilage as well as the bone tissues of the joints than not [11]. For similar reasons, it may be shown that adults who live in climates where the weather precludes outdoor activities for protracted periods may be more at risk than those in sunny climates, as may those in pain with low physical activity levels. In addition to failure of most studies to ascertain whether subjects were exposed to sunlight or not over the course of selected studies, plus the fact muscles around an affected joint might function sub optimally in the presence of low vitamin D-compounding the pathologic process, but that no outcome assessing any improvements in this realm were evident in the negative clinical studies, more comprehensive research in these realms is clearly desirable. As well, factors such as uncertain compliance with vitamin D regimens, and the use of monthly versus daily supplementation schedules [23], along with what constitutes suboptimal/excessive individual vitamin D dosages, suggests more carefully controlled studies with distinct inclusion criteria, as well as study protocols would be most helpful. The finding of 'no change' in status over a protracted period may also still represent a positive result in osteoarthritis, a progressive disease, as may the finding that after adjusting for age and gender, serum 25(OH)D showed statistically significant associations with most risk factors for knee

and hip osteoarthritis, other than injury [28], thus well designed research comparative studies with carefully construed experimental, sham and placebo control groups are highly desirable. However, most randomized controlled studies were not designed in this way in the past, nor were confounding factors such as extent of outdoor activity, climate, nutritional practices, supplementation and sunscreen usage, and factors such as ethnicity that can obviate improvements in vitamin D mediated joint status stringently controlled for in any prevailing study on this present topic in this author's view.

Conceivably, in recognition all these aforementioned factors, more carefully designed research studies appears to be the only way to resolve the present conflicting results. Most crucial in achieving this will be the use of more stringent universally adopted criteria for what constitutes vitamin D sufficiency or insufficiency, what an adequate study duration might look like, how vitamin D intake or vicarious exposure should be monitored, and what sample sizes are needed to permit conclusive results to emerge in longitudinal studies. As well, comparing groups with similar degrees of osteoarthritis pathology using valid indicators of cartilage viability is of high importance, given the lack of any definitive correlation between radiographic severity of osteoarthritis and pain, and the weak subjective elements in interpreting both these outcomes or baseline variables via survey instruments. What the optimum level of vitamin D should be-is also subject to discussion and is not a standard across countries or within countries, and consensus is needed about what might constitute the best method of measuring vitamin D intake, such as the use of serum samples, dietary records and questionnaires [28]. Co-morbid conditions that might affect vitamin D absorption, and changes to or reduced function of the vitamin D receptors that regulate vitamin D uptake and signaling might also prove especially worthy of exploration.

In closing, notwithstanding the laudable recent attempts to examine vitamin D as a correlate of articular cartilage in the context of osteoarthritis, we conclude the data base presently reviewed is equivocal and does not provide any conclusive evidence as to whether vitamin D is or is not beneficial as regards the prevention and treatment of people with osteoarthritis [51,60]. We believe however, that the idea put forth by Mabey and Honsawek [34] and Cao et al. [53] to conduct further research in this realm is still valid in light of the limited number of prevailing studies, the largely positive *in vitro* results, the presence of a fair number of clinical studies in support of a beneficial association of vitamin D and joint health, and some shortcomings of available studies presently reviewed [53-57].

In particular, only the knee joint has been studies in any systematic way, thus the question of how vitamin D interacts with hip joint cartilage in health and osteoarthritis should be studied more frequently to account for the positive findings of Lane et al [54]. This group showed low serum levels of 25-vitamin D to be potentially associated with incident changes of radiographic hip osteoarthritis as defined by joint space narrowing. To assist in solidifying the role of vitamin D in hand osteoarthritis, an area also completely discounted in the current data base, replicating the work of Soleva et al. Tetlow and Woolley, Garabedian et al. almost 40 years ago may be insightful [55,58,59]. Examining other joints such as the cervical and lumbar spine, ankle, elbow, and shoulder joints with reference to the possible role of vitamin D in the osteoarthritis pain cycle, and well designed research to differentiate between active forms of vitamin D supplementation, sham supplementation, and standard intervention will undoubtedly help to tease out actual versus placebo effects. More basic research to examine the impact of vitamin D on cartilage tissue from an array of joints at different levels of exposure is also likely to help establish what the most optimal levels for promoting cartilage integrity in clinical practice might be.

Until then, clinicians might need to base their recommendations on a careful evaluation of their individual client's demographic profile, their activity profile, their use of vitamin D supplements and their nutritional intake, as well as their health and osteoarthritis status. Those in the early disease stages of osteoarthritis may not need vitamin D supplementation if they are active outdoors, not using sunscreen, and eating nutritious foods. Those living in cold climates, those who use sunscreen regularly, those with darker skin pigmentation, and those in the advanced disease stages may benefit from efforts to carefully assess and to regularly monitor vitamin D levels so that supplementation can be forthcoming accordingly to avert or allay any excess osteoarthritis pathology.

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