Vitamin D and Osteoarthritis: An Updated Clinical Summary and Review

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Conflicts of interest statement: The author(s) declare(s) that there is no conflict of interest regarding the publication of this paper.

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Received: January 22, 2021 Revised: February 13, 2021 Accepted: February 15 2021 Published online: February 28, 2021

ABSTRACT

BACKGROUND: Osteoarthritis remains the most widespread disabling musculoskeletal condition affecting the wellbeing of many older adults.

AIM: This work aimed to update and document findings published in the English language concerning what is known about vitamin D and osteoarthritis disease manifestations and progression, an area of research that has produced confusing results.

QUESTIONS: Specifically examined were: (1) Whether the presence of inadequate serum vitamin D levels predisposes an older adult to more profound osteoarthritis disability than adequate levels; and (2) Whether applying vitamin D as a supplement to older adults with osteoarthritis and coexisting vitamin D deficiencies is likely to ameliorate osteoarthritis disability in some way.

METHODS: To achieve the current aims, all relevant English language research reports published in the last 40 years, with an emphasis on data from January 1, 2018 up until January 16 2021, and located in the major data bases of PUBMED, Scopus, and Web of Science, were sought. A narrative depiction and synthesis of the key points that emerged from this diverse body of literature was then undertaken.

RESULTS: Findings showed that regardless of study type, a vitamin D deficit that may prevail in a fair proportion of older osteoarthritis cases may produce less than favorable results if the deficiency is not compensated for. However, very few studies are sufficiently well-designed and a number show no uniform consensus in this regard.

CONCLUSION: More well-designed research may help to more firmly establish the possible protective, reparative or aversive role of vitamin D in mediating osteoarthritis and whether supplementation is desirable in vitamin D deficient cases.

Key words: Aging Adults; Disability; Osteoarthritis; Outcomes; Supplementation; Vitamin D

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INTRODUCTION

Despite years of study, the joint disease known as osteoarthritis, a health condition affecting a high proportion of older adults continues to produce large scale personal and social costs, including immense pain, job losses or limitations, and a wide array of functional and psychosocial challenges. Strongly associated with destructive processes of one or more freely moving joints such as the knee and hip joints, the condition is often accompanied by various degrees of joint inflammation, muscle weakness, joint instability, and joint stiffness. In addition, obesity, cardiovascular and metabolic health
comorbid health conditions, poor mental health including depression and anxiety, as well as low life quality and frailty alone or in tandem may prevail in older adult populations with osteoarthritis of one or more joints[11-19]. As well as being more prone to multi morbidities than healthy older adults, more recent evidence shows older adults with osteoarthritis are found to be at risk not only for functional disability but for acute respiratory disease manifestations in the face of the current COVID-19 pandemic and lockdown situations, including service shutdowns[30].

In a search for strategies to retard, prevent, or ameliorate one or more features of osteoarthritis disability, which has become more pressing than ever in efforts to minimize COVID-19 susceptibility and adverse outcomes, as well as the extent of the osteoarthritis disease itself, the role of vitamin D, a vital steroid hormone and mediator of bone and cartilage metabolism, as well as the immune system that is not manufactured by the body, has recently been discussed as a possible highly influential factor in this regard[24-36], but with no definitive conclusion being reached[37].

Since there is no prevailing remedy for successfully reversing osteoarthritis disability, and many cases requiring treatment may now have to be placed on hold during pandemic lockdowns, and lockdowns may limit vitamin D sunlight exposure sources in their own right, efforts to explore options other than traditional pharmacologic and surgical approaches to mitigating this condition, such as vitamin D supplementation appear warranted and supported at this time[29-17]. However, since contradictory evidence prevails, this present report strove to further examine what we know as of the onset of 2021 about vitamin D and osteoarthritis as a disease mediator.

Unfortunately, while several groups have tried previously to synthesize the knowledge gained on this topic, the topic remains unresolved, despite its possible promise for advancing our adjunctive intervention approaches. To avoid overlooking salient clinically relevant facts or evidence that may have emerged recently, an update on what we know at the start of 2021 was hence deemed to be of value.

METHODS

To obtain the desired evidence base, the key search terms currently applied were Vitamin D and Osteoarthritis. The currently accepted sources of information included clinical studies with cross-sectional designs, controlled studies, or those based on prospective research designs. The key database consulted was PUBMED.

While the search included data from 1980 onwards, the current search focused primarily on the retrieval and examination of data extending from January 1, 2018, to mid January, 2021 as a prior study conducted in the various lab settings and osteoarthritis models, nor clinical studies do exist-which is often not the case- observations conducted in the clinical setting are not currently comparable to those conducted in the various lab settings and osteoarthritis models, nor universal in agreement about their observations.

For example, while some who have focused on vitamin D deficits imply these may be linked to osteoarthritis in some way[15-17], supplementary vitamin D may have no meaningful clinical benefits[33,34], and may increase osteoarthritis pathology if serum levels are considered ‘excessive’ according to some[37]. On the other hand, it seems that a high percentage of hip or knee osteoarthritis cases are likely to exhibit low- rather than adequate- vitamin D serum levels[38-41]. They may also incur a greater risk for osteoarthritis progression[42], osteoarthritis disability, and pain as observed by some[38,43] but not others[44,45].

This is potentially confusing because consistent with a wide array of laboratory-based observations[16-18, Wang et al[46] observed that the administration of a high monthly dose of supplementary vitamin D appeared to successfully ally joint swelling in cases with knee osteoarthritis, as well as predicting the extent of any cartilage loss[41]. Men with hip osteoarthritis are also shown more likely than not to exhibit vitamin D deficiencies[46], a situation that may arguably increase rather than decrease or fail to have an effect on the rate of disease progression and joint space narrowing[48-50]. On the other hand, Ding et al[47] who assessed a broad range of vitamin D levels, rather than any predefined cut-off points, were able to conclude that achieving vitamin D sufficiency may prevent and/or retard cartilage loss in cases of knee osteoarthritis, a conclusion that concurred with that of Chaghanti et al[47], Yoshimura et al[51] on the other hand, observed no clinically relevant linkage between vitamin D levels and those knee osteoarthritis variables they assessed.

Emerging evidence also show that[48] cases undergoing joint revision surgery for end stage osteoarthritis and who are found to have low vitamin D levels are more likely to experience 90-day complications as well as periprosthetic joint infections after surgery than those with adequate levels, a situation that may affect up to 84% of surgical candidates[48]. They may suffer several independent overlapping osteoarthritis related problems as well[49-52], especially the risk of excess suffering and joint dysfunction[13,79]. Consequently,
efforts to ensure vitamin D levels are adequate, but not excessive, while at the same time, examining the premises behind the delivery of recommended doses that may be too low\(^\text{[81]}\), may help to mitigate osteoarthritis progression both within a joint as well as the "spread" of osteoarthritis from one joint to the next\(^\text{[82]}\). It may also lessen excess pain sensitization to the extent that opioids could be discontinued or surgery delayed, even in cases where only a single joint is affected, despite negative findings of Cakar et al\(^\text{[83]}\) who found subjective pain measures of 149 knee osteoarthritis cases, were not affected by degrees of vitamin D presence, although most cases studied were deficient in this vitamin. In addition to muscle related benefits\(^\text{[84,85]}\), vitamin D may help prevent pain\(^\text{[81]}\) and inflammation\(^\text{[86]}\), muscle function and sensitivity, plus life quality\(^\text{[87-89]}\). Moreover, conceivably, even if vitamin D does not alter structural features of osteoarthritis, if its presence maintains the status quo, or helps to maximize strength capacity\(^\text{[90]}\), this alone could be considered beneficial in the context of this progressive degenerative disease. Other benefits that should not be overlooked include a lower falls prevalence rate that may help avert the onset or increase of prevailing osteoarthritic joint damage, plus lower than desired levels of outdoor activity and sunlight exposure\(^\text{[91]}\). In addition, recent work further shows that cases with severe knee osteoarthritis and co existing diabetes can yet experience better glycemic control over time in response to either 800IU or 2000IU of vitamin D3 applied over a period of two years\(^\text{[92]}\). These beneficial findings and others may be important to examine further, because it is also possible that osteoarthritis exacerbates the availability of adequate vitamin D serum levels in its own right, for example due to its impact on weight gain and subsequent development of obesity where fat cells are found to "attract" vitamin D and reduce its availability\(^\text{[93]}\). Obesity, plus associated low levels of vitamin D, may in turn, promote, rather than inhibit inflammation, pain, and muscle weakness, thus producing more unwarranted and extensive progression of any prevailing cartilage and bone damage\(^\text{[94]}\). For similar reasons, it may be shown that adults with osteoarthritis who live in climates that are quite sunny, may still be vitamin D deficient in the event their pain and disability renders them depressed, sedentary, and home bound. Low levels of vitamin D are also linked to COVID-19 risk, as well as cardiovascular related syndromes, that can further preclude outdoor activities for protracted periods, while heightening muscle weakness and mobility challenges, thus reducing the general circulation of prevailing vitamin D within the body. Those cases advised to use sunscreen, masks, braces, splints, or gloves, plus those using wheelchair devices, or protective clothing might also be subject to lower than desirable vitamin D sunlight exposure\(^\text{[95]}\), and its potential for fostering adverse muscle and bone health consequences\(^\text{[96]}\). In sum, while several researchers imply there is no added value to recommending vitamin D supplementation in the context of osteoarthritis pathology, even if vitamin D levels are deficient\(^\text{[97]}\), and that such an approach may even do more harm than good, this conclusion is not universal. On average, however, even if this is only due to publication bias, the numbers of important clinically relevant findings that do exist appear to outweigh the negative or null results that prevail. In addition, unlike many areas of osteoarthritis intervention research, a fairly strong rationale and body of preclinical as well as clinical evidence prevails to support hypothesizing a contributory, moderating or mediating association between vitamin D and osteoarthritis joint damage, and its possible severity amelioration, at least in some cases, if not all. Indeed, even though very few joints have been studied as a whole, this linkage between vitamin D and some aspect of the osteoarthritis pain cycle, the symptom of most concern to patients, is especially hard to refute in light of the prevailing data and the nature of methods used to discern pain attributes. Another understudied correlate is muscle strength and performance.

Specific confounding factors at present are: (1) Discrepant and/or arbitrary follow-up periods in prospective studies; (2) Failure to control for presence, number, and type of chronic conditions; (3) Unknown medication usage rates, and types of medication usage; (4) Supplement usage; (5) Degree of outdoor activity; (6) Numbers and types of affected joints; (7) Extent of and type of any co-interventions; (8) Disparate and/or insensitive outcome assessment measures; (9) Limited attempts to measure biomechanical disease correlates objectively.

In particular, very few studies have carefully examined the presence of any associated joint inflammation or effusion, the prevailing sleep quality of the individual, the extent of any centralized pain, depression, muscle dysfunction or balance problems, obesity, frailty and falls history, or whether any of these overlapping aspects of osteoarthritis pathology were improved, or regressed consequent to vitamin D supplementation as can be argued might well be highly influential.

Consequently, even if vitamin D has no direct role in producing osteoarthritis, and does not appear to correlate with radiographic structural features of an osteoarthritic joint readily\(^\text{[98]}\), suboptimal serum levels of vitamin D may still be instrumental in increasing the magnitude of the disability, including the intensity of knee and hip pain\(^\text{[27]}\), health correlates that are detrimental to joint status, such as cardiovascular disease, and the negative effects of mechanically loading the diseased joint\(^\text{[99]}\). Conversely, even if vitamin D measures take time to implement and process, and are not favored by all\(^\text{[38,97]}\), more specific attention by practitioners to routinely assess their patient’s prevailing serum vitamin D status is expected to be more helpful than not in efforts to attenuate a measurable degree of their musculoskeletal disability\(^\text{[96,99]}\) and possibly even to their symptomatic as well as structural pathologies\(^\text{[100]}\). In particular, older persons with comorbid conditions that involve the kidneys, liver, skin, and gastrointestinal pathways who may be at higher risk than younger persons with no similar comorbid conditions, and unresponsive to recommended levels of oral vitamin D or sunlight exposure might be preferentially targeted. In addition, inquiring whether they are likely to be exposed to sunlight or not, whether they are able to obtain vitamin D food related levels of the vitamin, and efforts to stress the importance of consistent daily exposure or optimal vitamin D supplementation will also be more helpful than not in all likelihood, as may the delivery of optimal methods of vitamin D supplementation, and periodic serum vitamin D level assessments.

**DISCUSSION**

This work, which attempts to update prior work, has observed the findings of prior work to remain the same, with few exceptions. That is, very little progress has been made of late, and thus the merits of most of the research conducted for 40 years has still not resulted in better clinical practices or osteoarthritis outcomes for this progressive disease. While the hypothesis that on balance, that more good than harm can come from supplementing deficient vitamin D cases\(^\text{[85]}\), this is not mainstream or accepted practice. Contributing here are possible vitamin D fluctuations due to poor patient adherence, as well as differences in joint and mobility, alterations in health and mental health status\(^\text{[100]}\), the fact that obese cases may need higher doses of supplementation\(^\text{[101]}\), coupled with the persistent use of subjective
In the interim, notwithstanding the highly commendable recent any aspect of osteoarthritis pathology, and applying different on a single occasion. Determining how long it would take to impact where very high supplementary vitamin D doses are administered. Deleterious outcomes and their causes should also be sought, noted by Brennan-Speranza et al.

Function of the vitamin D receptors that regulate vitamin D uptake does some concerted universal consensus across or within countries, how often these should be applied clearly also warrants attention, as of these osteoarthritis correlates are indicated. What the optimum correcting ‘deficient’ vitamin D levels yields changes in one or more of vitamin D across the various stages of the highly debilitating basic research that examines the impact of vitamin D on osteoarthritis, requires study to eliminate misconceptions that could be costly if benefits are overlooked, or harm is caused inadvertently. Crafting more comparable carefully controlled and adequately powered research studies across different laboratories and settings, especially the community setting, and focusing on muscle responses to vitamin D may help immensely to uncover important clinically relevant intervention and prevention implications. To this end, more basic research that examines the impact of vitamin D on osteoarthritis joint structures other than articular cartilage, along with trials that examine varying degrees of structural integrity and how the degree of pathology influences the findings, may help clarify the importance of vitamin D across the various stages of the highly debilitating osteoarthritis pain and disability cycle, or explain the reasons for failure as well as successes in supplementation studies.

In the interim gaps in the literature include: (1) Efforts to examine reasons for conflicting study results depicted in Table 1 and others; (2) Lack of efforts to examine age, gender, pain, frailty, chronic inflammation, extent and degree of activity, musculoskeletal and health status, body mass impact osteoarthritis vitamin D -associations. At the same time, special attention to the extent of any prevailing biomechanical derangement, the role of vitamin D receptors (VDR), injurious work-related or daily activities and others, and bone health status issues, along with degree of exposure to sunlight and foods containing vitamin, are indicated. Moreover, careful efforts to monitor adherence to any self-administered vitamin D supplements, and overall health recommendations is equally essential.

**CONCLUSION**

Even if discounted by some, a role for vitamin D in the osteoarthritis pain cycle cannot be ruled out at present with any degree of confidence. As well, promising results from prospective studies as well as a host of observational studies prevail.

Maintaining optimal vitamin D levels is more likely than not to offset both excess osteoarthritis disability as well as its COVID-19 linkage among older adults, commonly at high risk for low serum vitamin D levels.
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Table 1 Table depicting most representative clinical investigations conducted prospectively over time in the context of examining linkages between vitamin D and osteoarthritis (OA) and showing little variability in type of osteoarthritis studied, but high variability in sample sizes, and conclusions among the studies [*no or adverse vitamin D-osteoarthritis effect demonstrated].

<table>
<thead>
<tr>
<th>Researchers</th>
<th>Study Approach</th>
<th>Study Sample</th>
<th>Key Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arden et al. [36]</td>
<td>3 year double blinded randomized placebo controlled trial performed at 5 UK hospitals</td>
<td>474 bilateral knee OA patients received 800 IU oral vitamin D or placebo daily for one year</td>
<td>Found radiographic progression over 3 years in the ‘contra-lateral’ knee, pain, stiffness, function were not improved</td>
</tr>
<tr>
<td>Bassioune et al. [65]</td>
<td>Prospective 12 months study</td>
<td>18 subjects with and without knee OA matched for age, gender, and body mass were observed</td>
<td>Vitamin D levels were significantly decreased in the subjects with knee OA</td>
</tr>
<tr>
<td>Bergink et al. [70]</td>
<td>Prospective cohort study</td>
<td>1248 cases of knee OA underwent baseline, vitamin D dietary intake assays and serum levels measures</td>
<td>Low dietary vitamin D intake increases the risk of progression of knee OA</td>
</tr>
<tr>
<td>Chaganti et al. [47]</td>
<td>Prospective study conducted over a 4.6 year time period</td>
<td>1104 elderly men with hip OA were followed</td>
<td>Men with vitamin D deficiencies are at high risk for hip OA, and twice as likely to have prevalent hip OA</td>
</tr>
<tr>
<td>Felson et al. [64]</td>
<td>Examined vitamin D levels in subjects longitudinally</td>
<td>There were 715 subjects in one study and 277 from another who were examined for vitamin D levels and radiographic worsening, but most knees had no evidence of OA at baseline</td>
<td>Vitamin D status was unrelated to the risk of joint space narrowing or loss of knee joint cartilage</td>
</tr>
<tr>
<td>Hussain et al. [37]</td>
<td>Prospective multiyear study</td>
<td>9135 adults who had vitamin D levels assessed in 1999-2000 and were 40 years or older undergoing hip arthroplasty for OA between 2002-2011</td>
<td>Increasing serum vitamin D levels were associated with an increased risk of hip arthroplasty in males, but not in females</td>
</tr>
<tr>
<td>Jin et al. [35]</td>
<td>2 year randomized controlled trial, where 209 subjects received monthly oral vitamin D treatments, 204 with knee OA did not</td>
<td>There were 413 completers of the study, all with initial low 25-hydroxyvitamin D levels, who had symptomatic knee OA</td>
<td>Monthly treatment with oral vitamin D (50,000 units) does not produce significant clinical or cartilage volume structural differences in vitamin D deficient knee OA cases over time</td>
</tr>
<tr>
<td>Konstari et al. [74]</td>
<td>Prospective Finnish based multi year study</td>
<td>805 healthy participants with no hip or knee OA underwent baseline and follow-up clinical examinations at intervals of 20-23 years</td>
<td>There is no association between serum vitamin D levels and the risk of incident knee or hip OA.</td>
</tr>
<tr>
<td>Konstari et al. [45]</td>
<td>10 year prospective cohort study</td>
<td>Knee and hip OA were diagnosed using a standardized clinical examination at baseline and follow-up.</td>
<td>However, there is a significant interaction between season of blood draw and serum vitamin D</td>
</tr>
<tr>
<td>Lane et al. [49]</td>
<td>8 year prospective cohort study</td>
<td>Covariates, included age, sex, season of blood draw, education, body mass index</td>
<td>The relative odds of developing definite knee OA in the winter season was 1.57 (1.10-2.27), whereas for the summer season it was 0.53 (0.28-1.00)</td>
</tr>
<tr>
<td>Manoy et al. [56]</td>
<td>Prospective study with 6 month follow up</td>
<td>Serum vitamin D concentrations were determined from baseline serum samples kept frozen at -20°C.</td>
<td>Monthly treatment with oral vitamin D (50,000 units) does not produce significant clinical or cartilage volume structural differences in vitamin D deficient knee OA cases over time</td>
</tr>
<tr>
<td>Sanghi et al. [77]</td>
<td>1 year randomized controlled trial pilot study</td>
<td>Results of 126 revision total joint arthroplasty patients between 2010 and 2014 were examined</td>
<td>There is a small clinical benefit to using vitamin D as regards pain and subjective functioning</td>
</tr>
<tr>
<td>Wang et al. [46]</td>
<td>Prospective 24 months randomized trial</td>
<td>1384 cases with osteoporosis or OA were followed for 3 years</td>
<td>Use of physician diagnosed OA may have been problematic</td>
</tr>
</tbody>
</table>

1419
418 knee OA patients

Yoshimura et al. [52]†
3 year follow up study
413 knee OA cases, divided into 3 groups, of vitamin D; insufficiency [<50 nmol/L at 3+24 months], fluctuating [>50 nmol/L at either 3/24 months], and sufficient levels [>50 nmol/L at 3+24 months]. In addition to vitamin D measures at 3+24 months, pain measures, effusion-synovitis and various cartilage and bone measures were conducted
Higher serum vitamin D levels do not prevent knee OA or lumbar spondylosis based on survey responses

Zhang et al. [48]
Prospective
209 knee osteoarthritis cases with vitamin D deficits received 50,000 oral IU for 24 months
Approximately 16% sample had low vitamin D levels. Between baseline and follow-up 15% progressed in joint space narrowing score responses

Zheng et al. [54]
Prospective 24 month cohort study-secondary analysis
200 participants from one site mean age 63±3 years, were randomly selected for measurement of serum levels of inflammatory and metabolic biomarkers at baseline and 24 months using immunoassays
There were no systemic metabolic or anti-inflammatory effects of note at any vitamin D level in the vitamin D deficient cohort or sufficient cohorts

Zheng et al. [87]†
Post-hoc analysis of a 24 month intervention trial
Individuals deficient in vitamin D have an increased risk of knee OA progression compared with those with greater vitamin D serum concentrations

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