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Research Article

Vitamin D and Osteoarthritis Pain

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Abstract

Effectively treating the pain accompanying osteoarthritis, a chronic irreversible progressively disabling joint disease remains extremely challenging. This mini review examines the controversial literature pertaining to: 1) whether vitamin D, a powerful bone-mediating compound involved in many physiological processes can influence the pain experience of people with osteoarthritis, and 2) whether more research in this realm is indicated or not. To this end, a comprehensive overview of relevant English language research reports published largely over the last five years was undertaken. The results showed that as with prior findings, those published since 2015 provide some conflicting evidence as regards a possible protective, reparative or mediating role for vitamin D in the context of osteoarthritis pain. However, in light of a substantive number of favorable findings, and feasible mechanistic explanatory mechanisms of action, it is concluded that further well-designed research and application of the wealth of supportive preclinical findings to the clinical realm may yet prove highly beneficial in this respect and is strongly encouraged.

Introduction

Painful disabling osteoarthritis, the most prevalent joint disease, remains highly impervious to effective amelioration in response to current non-pharmacologic treatment approaches such as exercise, weight loss, physical aids, and education, despite years of application and research in this regard. Moreover, several

non-surgical pharmacologic treatment approaches used to reduce osteoarthritic pain have not only failed to impact the disease and its progression to any known degree, but may well be contraindicated for long-term use in light of: their potentially toxic or fatal side effects [1], their potential association with an increased risk of cardiovascular events [2,3], and adverse, rather than desired health outcomes [4]. Death following excess opioid usage to quell osteoarthritis pain is also increasing. In addition, some recently tested biologically oriented therapeutic approaches have similarly failed to slow the rate of osteoarthritis joint space narrowing and/or were withdrawn before study completion in some cases [5]. In other cases, certain anti-inflammatory drugs, still advocated for treating osteoarthritis, have been shown to hasten, rather than slow the disease process, while some drugs that may impact joint space narrowing favorably, may not reduce pain [5]. Moreover, most treatment approaches currently recommended for treating osteoarthritis, even if independently efficacious, often neglect to consider the complexity of the disease and its impact on, plus involvement of, surrounding joint tissues, as well as its multifaceted cognitive and metabolic correlates. Additionally, too, its molecular and biomechanical pathogenesis is often discounted in the context of attempts to both understand the sources of, as well as the means of alleviating osteoarthritis pain [2,5]. On the other hand, a strategy that can favorably influence the structural and functional properties of articular cartilage, as well as the surrounding bone, muscles and nerve supply, plus inflammation, in a positive way, while safeguarding or helping to foster overall physical and mental health, would be highly valued in the context of osteoarthritis pain relief or its prevention, given the disease affects both the whole joint, as well as its spinal and central nervous system connections.

In this regard, vitamin D, a well-established steroid based hormone with a variety of biologically proven tissue-based impacts [6], including chondrocyte extracellular matrix synthesis [7] and bone homeostasis [8], as well as having broader behavioral and neurological effects [9], muscle physiology [10], and functional mobility effects [11], crucial to the maintenance of the skeleton and possibly to its associated tissues and body systems [2] is also reported to be a factor in the context of skeletal pain [12]. Moreover, its ability to foster multiple enzymatic processes, and decrease inflammation [13], while influencing bone and cartilage chondrocyte metabolism favorably may prove more helpful than not in preventing or attenuating osteoarthritis disease processes and their negative painful and disabling consequences, as implied by Pascual-Garrido *et al*. [14] and Vaishya *et al*. [6]. However, much controversy prevails in this regard, with no conclusions either favorable or unfavorable as regards osteoarthritis pain.

Aims

In light of the immense global burden of painful osteoarthritis, an incurable chronic disease disabler affecting many aging adults, this mini review, which builds on previous analyses was designed to continue to examine the extent of support for the idea that vitamin D, an established mediator of bone biology, growth, and development, as well as chondrocyte metabolism, and muscle function, may be an influential modifiable factor in the context of efforts to minimize, modulate or mediate osteoarthritis pain or a pain directly or indirectly or both in selected cases. Although previously studied, given the discrepant findings that continue to prevail, a secondary aim was to establish whether further research in this realm is warranted given the persistent burden of the disease and the purported role vitamin D plays in many essential life-affirming biological processes, including metabolic and neurological processes, sleep disorders and chronic pain [15,16].

Methods

To achieve these review aims, available documents housed in PUBMED and Web of Science Consolidated over time periods January, 1 2015-March, 31 2020 were sought using the key terms Vitamin D and Osteoarthritis Pain, or Vitamin D Deficiency and Osteoarthritis Pain.

To this end, all articles posted were first scanned for relevance, and only salient research articles or reviews that addressed some aspect of the current topic of interest was then reviewed in more depth. An attempt was made to include all modes of experimentation, although the focus was on clinically-derived data. It was determined that a systematic review was not suitable for examining current trends in the prevailing research due to its heterogeneity and limited volume and lack of any substantive well-conducted longitudinal research. While it is acknowledged the body of data presently reviewed may not be exhaustive-it was sought in an effort to highlight trends in this regard, given the prior lack of consensus on this topic. Readers wishing to explore prior reviews are directed to Vaiyshya *et al.* [6], Heidari *et al.* [16]' Diao *et al.* [17] and Gao *et al.* [18]. Articles of specific interest published in the last 10 years were included if they offered unique insights.

Results

As of March 31, 2020, the databases examined revealed only a small number of relevant studies, if compared to other research related themes research [See Table 1]. Moreover, despite the numbers highlighted below, many studies found listed in the context of vitamin D and osteoarthritis pain were not eligible for inclusion in this report, as they were clearly proposals, foreign articles, or abstracts, not full length papers, or focused on rheumatoid arthritis or osteoporosis. This small number of vitamin D related studies published in the last five years that focused on osteoarthritis pain and recounted in this review, which was largely the same regardless, of source examined, included a very limited number of either cross-sectional or longitudinal clinical research reports, plus a few preclinical reports, with no unifying or consistent theme, regardless of data base examined. Moreover, diverse approaches to the prevailing studies, including some studies focusing on deficiency effects of vitamin D in osteoarthritis, some on its possible pain associated effects, some on its unsafe supplementary effects, despite its generally favorable bone and joint structural effects, and muscle and inflammatory effects as well as its post surgical effects were more evident than not. As well, as in other areas of similar research, studies were either mostly favorable in support of vitamin D supplementation, if required, or unfavorable, and most were stand alone studies that did not attempt to truly build on past observations.

Table 1: *Summary of numbers of citations listed at key data bases over past five years (2015-2020)*

Keywords	Source	
	PUBMED	Web of Science [5 databases]
Osteoarthritis	27140	43117
Osteoarthritis + pain	9459	14971
Vitamin D + pain	500	561
Vitamin D + osteoarthritis	738	1271
Vitamin D + Osteoarthritis Pain	172	356
Vitamin D Deficiency + Osteoarthritis Pain	71	129

In sum, even though bone, skeletal muscle, and cartilage may be impacted independently or interactively by vitamin D, and this outcome may be implicated in the context of osteoarthritis pain production, the association between vitamin D and the current data focusing on the linkages between vitamin D and pain associated with an osteoarthritic joint is very hard to appraise systematically with any degree of confidence in this author's view. The narrative review below however, discusses the most recent articles favoring versus those that do not favor a role of vitamin D in pain control contexts in osteoarthritis, while offering some suggestions for the future based on these data.

Articles Favoring an Osteoarthritis Pain Vitamin D Link

In line with various preclinical studies implicating a potential role for vitamin D in osteoarthritis related pain mechanisms [eg 19,20], selected researchers such as Tague *et al*. [21] continue to claim that individuals experiencing musculoskeletal pain are more likely than not to be vitamin D deficient. In this regard, these researchers note that pain-sensing nerves, which are found to express vitamin D receptors, are likely to be responsive to suboptimal levels of vitamin D. They further report that they specifically observed that rats, often used as a model to highlight osteoarthritis and other disease mechanisms, who received vitamin D-deficient diets for 2-4 weeks exhibited significant muscle hypersensitivity in response to mechanical stimuli. Muscle hypersensitivity accompanied by balance deficits was also observed and occurred before the onset of overt muscle or bone pathology. The muscle hypersensitivity was not due to hypocalcemia and was actually accelerated by increased dietary calcium. Morphometry of skeletal muscle innervation showed increased numbers of presumptive nociceptor axons (i.e. peripherin-positive axons containing calcitonin gene-related peptide-a peptide involved in pain production), without changes in sympathetic or skeletal muscle motor innervation. Similarly, since the researchers found no change in epidermal innervation, it appeared that the vitamin D deficiency affected the musculoskeletal system components of the experimental rats differentially. In studying this set of observations further using a culture medium, Tague *et al*. [21] did indeed find that the sensory neurons that displayed enriched vitamin D receptors were affected by differing vitamin D concentrations. These aforementioned very interesting findings appear to indicate that the presence of a vitamin D deficiency can lead to selective innervation alterations that result in dose dependent pain-associated innervation changes in skeletal muscle, which in turn, may contribute to muscular hypersensitivity and pain, as is found in osteoarthritis.

In another study, Tague and Smith [22] discussed the additional idea that a vitamin D deficiency is associated with an increased susceptibility to inflammatory arthritis, given that sensory and sympathetic synovial nerves critical to the development of inflammatory arthritis and that spontaneously degenerate in the early phases of disease are nerves that contain vitamin D receptors. As well, they argued that vitamin D not only influences nerve growth, but neurotrophin expression as well. To validate these claims, these authors examined the density of synovial nerves and neurotrophin-containing cells in vitamin D-deficient rats. To this end, seven-week-old Sprague-Dawley rats were fed either control or vitamin D-deficient diets for 4weeks. Knee synovium sections extending from the patella to the meniscus were immunostained for total nerves, myelinated and unmyelinated nerves, sympathetic nerves, peptidergic and non-peptidergic sensory nerves, and neurotrophins and immune cell markers. In control rats, intimal innervation by unmyelinated sensory fibers was denser than subintimal innervation. In contrast, sympathetic innervation was confined to the subintima. Many sensory axons contained markers for both peptidergic and non- peptidergic nerves.

Nerve growth factor was primarily expressed by intimal CD163-negative type B synoviocytes, while neurturin, a ligand selective fornon-peptidergic sensory neurons, was expressed by synovial mast cells. In vitamin D-deficient rats, there were significant reductions in sensory nerves in the intima and sympathetic nerves in the subintima. While there was no significant change in nerve growth factor-immunoreactivity, the number of neurturin-expressing mast cells was significantly reduced in the intima, suggesting that intimal reductions in sensory nerves may be related to reductions in neurturin.

Vitamin D deficiency therefore may increase susceptibility to inflammatory arthritis, by depleting sensory and sympathetic synovial nerves as a result of reduced synovial neurotrophin content. In related recent work, and in support of some of the conclusions of Tague *et al*. [21], Poisbeau *et al*. [23] found that vitamin D supplementation improved mechanical nociceptive thresholds in monoarthritic animals and reduced mechanical hyperalgesia and cold allodynia in a model of mononeuropathy. Transcriptomic analysis of cerebrum, dorsal root ganglia, and spinal cord tissues indicated that the supplementation of vitamin D induced a massive gene dysregulation which, in the cerebrum, is associated with opioid signaling (23 genes), nociception (14), and allodynia (8), and, in the dorsal root ganglia, with axonal guidance (37 genes) and nociception (17). Among the identified cerebral dysregulated nociception-, allodynia-, and opioid-associated genes, 21 can be associated with vitamin D metabolism, whereby genes-Oxt, Pdyn, Penk, Pomc, Pth, Tac1, and Tgfb1-encoding for peptides/hormones stand out as top candidates to explain the therapeutic benefit of vitamin D3 supplementation. While experimental models may be criticized from several vantage points, the authors concluded that further studies of vitamin D and its ability to alleviate joint pain through objectively observed pathways are clearly warranted.

More recently, Li *et al.* [19] investigated the effects of vitamin D on articular cartilage degradation by testing the activation of a destructive enzyme called matrix metalloproteinase in articular cartilage using the rat vitamin D deficiency model. At the animal level and rat articular chondrocytes cell level results showed that the presence of a vitamin D deficiency increased the expressions of two forms of the destructive metalloproteinase enzyme, and that the increase in this enzyme and others was inhibited or significantly suppressed by vitamin D supplementation or treatment. In terms of pain, it was concluded that deficiencies in vitamin D intake may influence the production of destructive enzymatic activities within cartilage tissue and may hence influence articular cartilage degeneration and osteoarthritis disease progression.

In a related report that is potentially quite relevant to untangling the painful symptomology of osteoarthritis, Li *et al* [24] noted that if the biological effects mediated by vitamin D and the vitamin D receptors are compromised, and multiple pathophysiologic processes, including impaired calcium phosphorus metabolism, immune regulation, autophagy, vital to maintain energy and metabolism in cells, may be closely associated with various pathological processes such as inflammation, a major pain source in osteoarthritis.

In extending the above research to the clinic, a recent clinical study conducted by Thomas *et al*. [25], found vitamin D supplements to increase both serum vitamin D and pain scores of osteoarthritis patients. The vitamin D supplements also improved the subjects' general health.

The study was conducted for eight months among 142 patients with osteoarthritis and low vitamin D levels. An experimental group and a control group who were similar were studied. Percentage distribution of

positive changes was significantly higher in those with more severe disease and pain scores at follow-up compared to controls. These findings are generally consistent with those observed clinically by Alkan and Akgol [26] who found that knee osteoarthritis cases with vitamin D deficiency exhibited greater pain, as well as Veronese *et al*. [27] for the hand and joints in women, and Helde-Frankling and Björkhem-Bergman [28] for joint pain, in general among vitamin D deficient adults.

Conflicting Articles

In contrast to the aforementioned studies, Perry *et al*. [29] reported finding no vitamin D supplementation effect after two years in knee osteoarthritis cases, even though Manoy *et al*. [30] who studied 175 knee osteoarthritis cases with low levels of serum vitamin D found subjects to exhibit decreased pain, and improved function after vitamin D supplementation given each week in doses of 40,000 I.U. for 6 weeks. Glover *et al*. [31] too observed a link between vitamin D deficiency and pain sensitization in African-American patients with knee osteoarthritis, implying that certain subgroups may be at greater risk of pain than others due to inherent biological attributes.

Hung *et al*. [31] who examined dietary and supplemental vitamin D on knee osteoarthritis symptom severity found vitamin D to be positively associated with pain, however, even though it was strongly associated with lessened disability among the cross-sectional data set analyzed retrospectively data were also somewhat at odds with those of Zheng *et al*. [32] who found positive effects of maintaining vitamin D sufficiency in 413 knee osteoarthritis cases, and those of Mermerci *et al*. [33] who found no association of vitamin D levels with functional status in cases with radiographic knee osteoarthritis, even though 85% cases had low vitamin D levels, but no direct pain comparison between deficient and sufficient cases was forthcoming.

A favorable link between vitamin D supplementation or maintenance of an optimal dosage and depression symptoms, a common pain correlate in knee osteoarthritis, has also been observed [34].

Unsurprisingly, in a study by Lee *et al*. [35], where the prevalence of preoperative hypovitaminosis D (25-OHD <50 nmol/L) was 44% in osteoarthritis cases, there were transient higher pain intensity scores in the moderate-to-severe hypovitaminosis D (25-OHD <30 nmol/L) group compared with the sufficient vitamin D group. The incidence of moderate-to-severe persistent pain was 9%, and hypovitaminosis D increased the risk of moderate-to-severe persistent pain (adjusted odds ratio 2.64, 95% CI: 1.03-6.77). Preoperative hypovitaminosis D also had subtle effects on pain intensity scores in the early postoperative period and was deemed a risk factor for moderate-to-severe persistent pain after knee arthroplasty. An opposing result however, stemming from a case-control study of severe knee osroarthritis cases, found no statistically significant correlations between serum 25-hydroxy vitamin D level with WOMAC functional scores ($r = 0.102$, $P = 0.438$) and the grade of osteoarthritis ($r = -0.063$, $P = 0.630$) as well as between serum COMP and 25-hydroxy vitamin D levels ($P > 0.05$) [36]. Yet, a further recent review indicated that supplementation of vitamin D3 along with coconut oil could be an effective strategy for delaying the progression of knee osteoarthritis by reducing cartilage degeneration, inflammation and pain, as well as improving functional abilities [37] Jin *et al*. [38] however, found no effect of vitamin D on pain as one of the parameters studied in their symptomatic osteoarthritis knee cases, a study criticized in some technical respects by George [39], while Cakar *et al*. [40] concluded that pain in knee osteoarthritis is unrelated to vitamin D status, even

though their sample of 179 cases seemed deficient in 90 percent of the patients and quite high average pain scores were evident, and the reported incidence of low vitamin D was in the range of 25 percent in the population, and 40 percent in the elderly. Only 14 of their cases were considered to have normal vitamin D levels, thus statistically it is challenging to accept their results at face value in this cross-sectional study.

Moreover, subjects attending the clinic were not necessarily representative of the population, as most were women with modest radiographic changes. Mat *et al*. [41] argue however, that factors such as skin tone, diet, and sun exposure among other factors may confound the association between vitamin D status and osteoarthritic pain, and that more careful study in this respect is warranted.

Balogun *et al*. [42] for example, found no within person changes in falls risk relative to vitamin D although overall functional scores predicted falls, but this group did not study cases with defined osteoarthritis or clarify pain status clearly. Arden *et al*. [43] found vitamin D had no effect after three on joint space narrowing in a placebo controlled study, but was not able to assess all subjects who began the study over time. There was however, less reported pain in the experimental group, but more in the control group according to the authors after the three years, even though this was statistically non-significant. The results were also at odds with those of Yoshimura *et al*. [44] who found increased vitamin D levels over a three year period were associated with increases in bone mineral density in a large population based study, which demonstrates structural changes attributable to vitamin D can occur in the areas most related to osteoarthritis damage and pain production. Exposure to ultraviolet light, which may increase vitamin D levels, was also found to decrease pain in a sample studied by Harari *et al.* [45], while deficiency appeared to be a pathogenic factor in cases with medial tibio-femoral knee osteoarthritis studied by Bassiouni et al. [46]

In terms of explaining why vitamin D may influence osteoarthritis pathology and pain, Yamamura *et al*. [47] who investigated the effects of vitamin D on articular cartilage degeneration using eldecalcitol (ED-71), which is an active vitamin D3 analog, found joints of their animal model of osteoarthritis demonstrated slowed progression of the disease at 4 weeks after surgery, but few effects were observed at 12 weeks after surgery. Ets-related gene (Erg) expression was upregulated in the osteoarthritic articular cartilage, and further increased by ED- 71 treatment. In primary chondrocytes cultured with ED-71, the gene expression of Erg and lubricin/proteoglycan 4 significantly increased, as compared to that of cells cultured without ED-71. Local treatment with ED-71 reduced degenerative changes to the articular cartilage during the early phase of the experimental model of osteoarthritis. It was concluded that regulation of Erg by ED-71 in articular cartilage could confer resistance to early osteoarthritic changes.

Barker *et al*. [48] found vitamin D had no effect however, on circulating cytokines in the context of knee osteoarthritis, a finding similar to Zheng *et al.* [49] who reported no effects of vitamin D on inflammation among knee osteoarthritis cases.

Discussion

The impact of vitamin D, a steroid hormone with multiple physiological and metabolic associations, is proposed by some to impact neurosensory functions, including pain processing, and pain relief [23,28]. Osteoarthritis, a highly disabling incurable joint disease, involving multiple joint structures, and body

systems, and one where any form of palliative or reparative treatment that is non-toxic and encourages mobility, while reducing pain, would be highly prized, remains largely subject to pharmacologic and/or surgical interventions of varying degrees of efficacy and effectiveness, and a very confusing set of recommendations regarding the benefits a number of nutrients on pain processing, including vitamin D. Indeed, despite considerable background research on the importance of vitamin D in mediating cartilage and bone formation and status, cognitive and muscle function, as well as overall health status and quality of life [5] very little definitive research, especially favorable clinically oriented research, in any of these contexts has been forthcoming. Confusing findings and conclusions based on limited study numbers and design in the context of osteoarthritis per se [eg 50,51], the possible challenges associated with the control of vitamin D exposure, activity frequency and nature, plus confounders such as nutrients that contain vitamin D, render it challenging to tease out determinants of study outcomes in this realm, and may account for its limited overall support, despite a sound rationale for anticipating a highly salient role in mediating or moderating role osteoarthritis pain.

That is, despite a reasonably strong underlying core of preclinical as well as clinical data showing vitamin D is an important daily requirement for purposes of ensuring optimal joint as well as overall health status, and that persons with osteoarthritis and chronic pain may be at risk for either a reduced ability to take up vitamin D, for example, if they are not able to go outside, if they use sunscreen, are elderly, wear protective clothing outdoors, or have a greater need for this vitamin than those who are not subject to muscle and bone related joint changes, the application of these observations to the clinic remains non-conclusive at best.

Some of this uncertainty may stem from the fact that patients who do appear to benefit from vitamin D supplementation in some cases as regards pain as described by Helde-Frankling and Björkhem-Bergman [28], do not exhibit functional or structural benefits because the pain free patient now overuses the joint. In addition to that, the ability to utilize vitamin D may not be uniform in all groups, or across genders and ethnicities, the duration of the study may be too limited, the outcome measures may be insensitive or unreliable, and genetic variations in vitamin D receptors may account for the lack of uniformity several supplementation study responses

Moreover, the application of high vitamin D doses applied over time may indeed be toxic rather than therapeutic [38].

Challenges in identifying the sources of vitamin D discussed in some clinical studies, the failure to employ uniform modes of assessing baseline and outcome vitamin D values in prospective studies, plus unclear efforts to control for vitamin D exposure, activity levels, seasonal factors, ethnic and gender factors, along with the varying degrees of osteoarthritis pathology studied, and subjective pain reports of varying nature were common, regardless of study design are further obvious factors that may be influencing the ability to arrive at solid conclusions regarding this topic.

In addition, infrequent attempts to acknowledge the effects of history, exposure to sunlight, supplements, co-interventions, and use of foods containing vitamin D among other confounders, surely limits conclusions concerning the precise effect of vitamin D on osteoarthritis pain, as observed in preclinical studies.

Additional sources of persistent controversy may stem, in part, from differences in what is studied, for how long, from what joint[s] are studied, and whether the patient has multiple affected joints or single joint manifestations, mild, moderate, or severe disease. The role of chronic health conditions, pharmaceutical drugs to offset pain, cognitive health status, as well as health behaviors, and practices, and extent of outdoor activity, and activity type and magnitude, must surely be potentially confounding factors in this line of research.

However, some very promising findings in the realm of efforts to prevent or attenuate the highly resistant form of pain experienced by people with osteoarthritis [eg 16,52,53] have been forthcoming in the last five years, or it appears that while these may not prevail for all osteoarthritis cases, they may be clinically useful for intervening among selected osteoarthritis sub-groups [30,54,55], if not all subjects, thus case finding approaches may be helpful here.

Moreover, the possibility of employing carefully titrated vitamin D supplements as an adjunct for alleviating, minimizing, ameliorating, or treating osteoarthritis joint damage, including damage due to inflammation [29], and possibly muscle associated problems [26,56,57] in patients with low vitamin D levels, does seem possible, and should not be discounted without further research.

Indeed, in addition to the present research described in this review, a sizeable body of past research shows vitamin D may have multiple beneficial implications that may be especially valuable in minimizing or preventing neuropathic pain, depression, and sleep disturbances observed in osteoarthritis, and that heighten pain [23,59].

The observed additive effect of resistance training and vitamin D supplementation in older women adults [60], even if the pain effects are small [55] are further salient findings that should also not go unnoticed or be overlooked [61]. In addition, there are several noteworthy current findings that indicate favorable pain related vitamin D mechanisms of action on cartilage cells and joint tissues in increasing numbers of preclinical studies, if not clinical research [eg 19-21,32].

However, the translation of preclinical data in particular to the bedside will continue to be challenged by many obvious factors, such as multiple research design flaws, studies of short duration and the omission of studies that examine joints other than the hip or knee, unless a concerted effort is forthcoming. In this regard, more thought is encouraged regarding the role of baseline demographics, and disease manifestations and duration and extent, including the extent and nature of any prevailing pain, vitamin D serum levels, and nutritional practices, plus comorbid disease profiles, medication intake the nature of any supplementary osteoarthritis treatments. Efforts to control for sunlight exposure, and carefully delineated activity profiles along with adequately blinded subjects in supplementary related trials is also strongly indicated.

More attention to examining vitamin D in the context of muscle function and bone synthesis, major components of synovial joints, as well as examining its impact on pain mediators such as depression, anxiety, and sleep [58,61], cartilage chondrocytes [62], as well as bone metabolism [63] is likely to be insightful in this respect, as well.

Conclusion

Notwithstanding the idea that excessive exposure to sources of vitamin D should be avoided, the present data suggests that the maintenance of a sufficient level of serum vitamin D may not only help alleviate pain is some cases of osteoarthritis, that its deficiency may induce a neuropathic pain state [64], and impair muscle function and bone health [63,64]. A deficiency may further induce a higher pain intensity in subjects with chronic widespread pain than those with sufficient levels [65], as well less favorable outcomes among those undergoing knee arthroplasty surgery [66].

However, to translate these ideas to the clinic more effectively, it is clear more evidence that emanates from well-designed and thoughtful research in this regard is required. Moreover, based on related research by Li *et al.* [24] and Shaik-Dasthagirisaheb *et al.* [67], a role for vitamin D deficiencies in mediating or moderating inflammatory processes that can accelerate or magnify any prevailing joint destruction should be further explored. The specific role of vitamin D receptor gene polymorphisms [68], which has not been well explored, also appears to warrant specific attention.

In the meantime, since the addition of desirable amounts of vitamin D to the diet of vulnerable patients, where deficient, may yet help to mitigate the progression of the disease [69], while decreasing the need for long-term analgesia [24], even after surgery [70], this approach may also be especially helpful in cases with multiple health problems such as obesity [71], diabetes, anxiety, and depression [72], even if this idea is refuted by Jin *et al.* [40], Hussein *et al.* [73], and Cuellar *et al.* [74], among others [75]. Equally helpful may be further research to carefully examine the possible linkages presented in Figure 1, especially as applied to high risk osteoarthritis sub-groups with and without verifiable vitamin D deficiencies and muscle weakness, and to do this meticulously and rigorously to rule out competing hypotheses may be of additional help.

Emergent preclinical findings [76], and others [77-80], plus the failure of most current pharmaceutical approaches for alleviating osteoarthritis pain safely and effectively [81], imply efforts to examine the efficacy of tailoring doses for reducing osteoarthritis pain and moderating its development and its long term impact on joint structure and function in carefully selected sub groups will likely prove insightful and should be carefully examined by those who seek to further our ability to intervene favorably in minimizing the pain and its life negating effects among osteoarthritis cases [82].

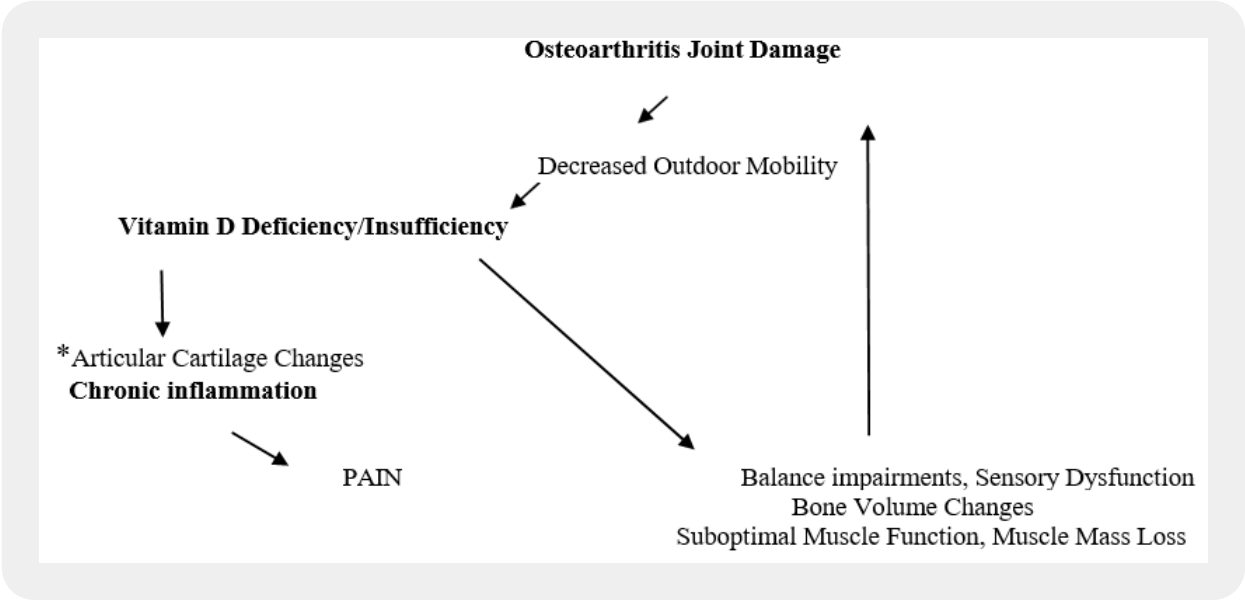

Figure 1: *Points* at which vitamin D or a lack thereof may influence the osteoarthritis pain cycle*

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