Vitamin D and Its Effects on Articular Cartilage and Osteoarthritis

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Background: Osteoarthritis (OA) currently affects 10% of the American population. There has been a recent push to determine exactly what causes OA and how it can be treated most effectively. Serum vitamin D levels have been associated with OA and may have an effect on articular cartilage remodeling.

Purpose: To critically review the published research on the effect of vitamin D on articular cartilage and the development of OA as well as on the mechanism behind cartilage regeneration and degeneration.

Study Design: Review.

Methods: A systematic search of PubMed and the Web of Science was performed for relevant studies published in the English language through April 30, 2016, using the terms vitamin D, articular cartilage, and osteoarthritis.

Results: On a molecular level, 1α,25(OH)2D3, the activated form of vitamin D, plays a role in articular cartilage degeneration. Vitamin D binds to vitamin D receptors, triggering a signaling cascade that leads to chondrocyte hypertrophy. In clinical trials, vitamin D deficiency poses a risk factor for OA, and those with decreased cartilage thickness are more likely to be vitamin D–insufficient.

Conclusion: The role of vitamin D supplementation in the treatment or prevention of OA remains uncertain. More research is needed to reconcile these conflicting findings.

Keywords: vitamin D; articular cartilage; osteoarthritis; 1,25-Dihydroxyvitamin D; vitamin D receptor

Osteoarthritis (OA) is the most common joint disorder in the United States.50 While there are some theories of the pathogenesis of OA, the exact mechanism is not well defined. One promising theory suggests that repetitive mechanical stimulation of articular cartilage prevents it from regenerating properly, which ultimately leads to cartilage degeneration. When traumatized, articular cartilage produces an anabolic response; however, as chondral wear accrues over time, the anabolic response in the articular cartilage declines and the imbalance between chondrocyte synthetic activity and degradative activity leads to progressive thinning of articular cartilage.10 Vitamin D has been associated with cartilage regeneration in OA, but the exact mechanism is not well defined. Vitamin D deficiency is associated with an increased risk of patients developing OA in some studies, but the results of other studies have been inconsistent. The purpose of this article was to summarize the role of vitamin D in articular cartilage physiology and OA and review the current literature that investigates the role of vitamin D in articular cartilage regeneration.

OSTEOARTHRITIS

Currently, symptomatic knee OA occurs in 10% of men and 13% of women aged 60 years or older.50 According to the Centers for Disease Control and Prevention, 1 in 2 Americans may develop symptomatic knee OA by the age of 85 years. In the obese population, 2 in 3 Americans may develop symptomatic knee OA in their lifetime. As the American population ages and the number of obese Americans increases, the number of people affected with symptomatic OA is likely to increase.20
To treat OA, various medical and surgical interventions can be performed to slow the progression of the disease but not cure it. For those with non-inflammatory OA, acetaminophen is given as needed. For those with inflammatory OA, nonsteroidal anti-inflammatory drugs (NSAIDs) are given in both oral and topical form. If NSAIDs do not work, intra-articular corticosteroids are given. For those in which non-operative management does not provide relief, surgery is suggested depending on which joint is arthritic. There are currently no disease-modifying drugs available for clinical use. There are some clinical trials for disease-modifying drugs, but more research is needed to determine the pathogenesis of OA to better treat patients in the future.

Articular Cartilage

Articular cartilage can withstand routine mechanical stress produced by the human body. It is an avascular and aneural tissue that is made up of chondrocytes within an extracellular matrix consisting predominantly of type II collagen, proteoglycans, and aggrecans. Articular cartilage is heterogenous, and its material properties change as a function of depth. Each layer contains a complex extracellular matrix made of proteoglycans, aggrecans, and type II collagen. The matrix is produced by chondrocytes, which are the only cells found in adult articular cartilage. These cells are responsible for remodeling and maintaining the structural and functional integrity of the cartilage. Chondrocytes in the superficial zone are densely packed cells that are oriented parallel to the articular surface. Within this layer, type II collagen is oriented parallel to the articular surface, allowing for increased tensile strength. Chondrocytes in the middle zone are round and are randomly distributed within the extracellular matrix, and chondrocytes in the deep zone are also round like those in the middle zone but form clusters. In the middle and deep zones, type II collagen is randomly distributed and oriented perpendicular to the articular surface, respectively, to allow for both layers to have compressive strength. Of note, both of these layers have increased expression of the tissue damage and release mediators that stimulate the formation of fibrillations, matrix depletion, cell clusters, and loss of articular cartilage and ultimately the presentation of pain as a symptom of OA.

Articular cartilage degradation involves a catabolic reaction that involves proteolytic degradation of the connective tissue matrix. Interleukin-1 (IL-1), which is synthesized by chondrocytes and mononuclear cells lining the synovium, acts in multiple pathways to suppress the synthesis of type II cartilage and to promote the formation of type I cartilage. It induces catabolic enzymes such as stromelysin and collagenase and suppresses prostaglandin synthesis. In addition, it acts with tumor necrosis factor–α (TNF-α) to inhibit synthesis.

Articular Cartilage and Osteoarthritis

Macroscopically, the earliest sign of articular cartilage degeneration is due to fibrillation of its superficial layers. As the disease progresses, the superficial surface irregularities form clefts, the articular surface roughens, and the fibrillations extend deeper into the cartilage until the fissures invade the subchondral bone. As the cartilage fissures deepen, the articular cartilage tears, and fragments are released into the joint space, leading to possible irritation. Eventually, enzymatic degradation of the matrix decreases the cartilage, leading to loss of articular cartilage and ultimately the presentation of pain as a symptom of OA.

Articular cartilage degeneration in OA can be broken down into 3 stages: cartilage matrix damage, chondrocyte response to tissue damage, and decline of chondrocyte synthetic response and progressive loss of chondral tissue. In the first stage, the matrix molecular framework is altered and water content increases. Two principal mechanisms are thought to initiate this stage. In most patients, damage to normal articular cartilage occurs by physical forces; this can be due to a single event of macrotrauma or repeated microtraumas. In response to these traumas, chondrocytes release degradative enzymes. In a smaller percentage of patients who have altered joint biomechanics, past inflammatory joint diseases, congenital abnormalities, or metabolic syndromes, genetically defective cartilage fails under normal joint loading, leading to OA. On a microscopic level, articular cartilage loses proteoglycan aggregation and experiences swelling, which leads to hypertrophy. In an attempt to regenerate the extracellular matrix, chondrocytes increase synthesis of types II, IX, and XI collagen, aggrecan, and type IV collagen, which is associated with the formation of fibrillations, matrix depletion, cell clusters, and loss of proteoglycans and cleavage of type II collagen that causes an increase in matrix content and leads to hypertrophy.

The second stage occurs when the chondrocytes detect the tissue damage and release mediators that stimulate a cellular response consisting of anabolic and catabolic activity and chondrocyte proliferation. In response to this stress, proliferating chondrocytes surround the newly synthesized matrix molecules and release chemical mediators such as nitric oxide, which diffuses and can induce production of IL-1. IL-1 is capable of inducing the expression of MMPs, aggrecanases, and other catabolic genes and cytokines such as A disintegrin and metalloproteinase with thrombospondin type 1 motif (ADAMTS)–4 and ADAMTS-5.
Expression of MMPs, especially MMP-13 and MMP-3, allows for the degradation of collagens II and IX and ultimately disruption of fibril function.44 Expression of ADAMTS-4 and ADAMTS-5 causes cartilage degeneration. In experiments with mice with single knockout of the ADAMTS-5 gene or double knockout of the ADAMTS-4 and ADAMTS-5 genes, lack of these genes prevented cartilage degradation in surgically and chemically induced murine knee OA models.51 IL-1 and TNF-α increase synthesis of prostaglandin E2 by stimulating the expression of cyclooxygenase 2, microsomal prostaglandin E synthase–1, and soluble phospholipase A2. In addition, IL-1 induces proinflammatory cytokines such as IL-6, leukocyte migration inhibitory factor (LIF), IL-17, IL-18, and IL-8.16 The presence of fibronectin fragments or other molecules in the damaged articular cartilage further increases the production of IL-1 and molecules produced downstream of it.10 As a result, chondrocytes undergo further phenotypic changes. Degradation of types IX and XI collagen and other molecules destabilize the type II collagen meshwork.10 The superficial zone is disrupted, and loss of aggrecan due to enzymatic degradation increases the stress on the remaining collagen fibril network and chondrocytes.10

The third stage occurs when the decline in the chondrocyte anabolic and proliferative response leads to progressive loss of articular cartilage.10 Eventually, the articular cartilage’s anabolic response declines, and the imbalance between chondrocyte synthetic activity and degradative activity leads to progressive thinning of articular cartilage.32 The thinning and ultimate loss of articular cartilage leads to the clinical syndrome of OA, characterized by joint pain and loss of joint function.10

VITAMIN D

Vitamin D deficiency affects 42% of the American population.15 Specifically, people who live in northern regions of the United States and those who remain indoors are most prone to deficiency.21 Once thought to cause solely rickets and decreased bone density, vitamin D deficiency has been associated with several chronic diseases such as multiple sclerosis, type I diabetes, and hypertension.22

People receive the largest proportion of vitamin D from exposure to the sun. When sunlight hits the skin, the ultraviolet radiation turns 7-dehydrocholesterol to pre–vitamin D3. Pre–vitamin D3 is then converted into 25-hydroxyvitamin D3 by the liver. In the kidney, 25-hydroxyvitamin D3 reacts with 25-hydroxyvitamin D-1α hydroxylase to become 1,25 dihydroxyvitamin D3 (vitamin D).22 It then enters the bloodstream, where it travels to tissues possessing vitamin D receptors (VDR) such as intestines, kidneys, bone, bone marrow, and chondrocytes.21 When vitamin D binds to VDRs, the complex binds to vitamin D3 response elements (VDREs) in the promoter region of various target genes.6,46

In particular, activation of VDRs results in the absorption of calcium to regulate the circulating levels of calcium and phosphate for normal mineralization of bone, both of which are also regulated by the parathyroid hormone.14 Specifically, when the levels of blood calcium are low, the parathyroid gland releases parathyroid hormone, causing expression of proteins that leads to an increase in total body calcium levels.45 In the kidney, parathyroid hormone induces the conversion of 25-hydroxyvitamin D to 1,25 dihydroxyvitamin D, which ultimately results in an increase in the transcription of genes responsible for calcium absorption.43 When the parathyroid hormone is removed, vitamin D cannot function properly within the patient, resulting in hypercalcemia. In order for a patient to have adequate and efficient blood calcium levels, both vitamin D and parathyroid hormone must be present at sufficient levels and function together.14 According to the National Institutes of Health, serum 25-hydroxyvitamin D concentrations should be greater than or equal to 20 ng/mL and less than or equal to 50 ng/mL.38 Concentrations less than 12 ng/mL are deemed deficient and could lead to rickets in children and osteomalacia in adults. Concentrations between 12 and 20 ng/mL are considered inadequate for bone health in adults. Concentrations greater than 50 ng/mL may lead to deleterious health effects.

VITAMIN D AND INFLAMMATION

Vitamin D is a key immunoregulator in the reduction of inflammation, and it has been shown to exert influence on T and B lymphocytes, macrophages, and dendritic cells.18 VDRs are present in immune cells, and when vitamin D binds to VDRs, VDREs are activated. Activation of the VDREs in the promoter region of cytokine genes blocks transcription of nuclear transcription factors such as NF-κB and NFAT (nuclear factor of activated T cells) and NF-κB.18 This interference blocks the cellular response to TNF-α and IL-1 and allows for the upregulation of IL-10.7 A recent study on vitamin D–deficient IL-10 knockout mice with inflammatory bowel disease showed that when mice were given vitamin D, their inflammatory bowel disease was mitigated due to the effect of vitamin D on TNF-α.54 In a murine colitis model, increase in IL-10 production by 1,25(OH)2D3 allowed for Treg (regulatory T cells) induction.12 Because of its anti-inflammatory nature, vitamin D is sometimes used as a medication for patients with chronic diseases such as rheumatoid arthritis, multiple sclerosis, and systemic lupus erythematosus.37 Further investigation, however, is needed to more fully understand the specific mechanisms by which vitamin D acts to reduce inflammation.

VITAMIN D AND ARTICULAR CARTILAGE

Recent evidence suggests that the role of vitamin D in the progression of OA is promising. Articular cartilage degenerates in OA patients due to a homeostatic imbalance in which catabolic processes overrule anabolic processes. As a result of this reaction, articular cartilage becomes hypertrophic and eventually deteriorates. Several studies have shown that VDRs are upregulated on damaged cartilage. Tetlow and Woolley47 showed that VDR expression is increased in areas of erosion in patients with late-stage rheumatoid arthritis. The same
research group and Orfanidou et al showed similar results in patients with OA. When vitamin D binds to VDRs, a signaling cascade effect occurs. Tetlow et al demonstrated that chondrocytes expressed increased levels of MMPs 1, 3, and 9 in vivo. This leads to degradation of bone at increased rates. VDRs also signal increase in fibroblast growth factor 23, caspase 9, and extracellular signal-regulated kinase 1/2. When VDR is inhibited, downregulation occurs. The upregulation of vitamin D signaling in an arthritic joint is the body’s response to joint degeneration through an attempt to spread joint contact pressures through new bone formation in the form of osteophytes, but it is unclear whether this is a positive or ultimately detrimental response. Future research should aim to investigate the extent and severity of these actions and their implications on the

| Authors          | Study Design | Sample Details                                                                 | Vitamin D Serum Level Measurements                                                                 | Finding                                                                                                                                 |
|------------------|--------------|---------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------|
| Zhang et al      | Prospective  | 418 knee OA patients had vitamin D levels measured                               | Vitamin D deficiency <20 ng/mL                                                                      | Patients deficient in vitamin D had an increased risk of knee OA progression compared with those with greater vitamin D serum concentrations |
| Heidari et al    | Prospective  | 148 patients with knee OA and controls had serum vitamin D levels assessed       | Vitamin D deficiency <20 ng/mL                                                                      | There was a significant association between serum vitamin D deficiency and knee OA in patients <60 y                                     |
| Goula et al      | Prospective  | 164 patients with knee or hip OA had vitamin D levels measured                  | Vitamin D deficiency <20 ng/mL                                                                      | 81.7% of patients were vitamin D deficient, 15.2% were vitamin D insufficient, and only 3% were vitamin D sufficient                      |

### TABLE 2

| Authors          | Study Design | Sample Details                                                                 | Vitamin D Serum Level Measurements                                                                 | Finding                                                                                                                                 |
|------------------|--------------|---------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------|
| Bassiouni et al  | Prospective  | 50 patients with and without knee OA were observed over a 12-month period        | Vitamin D deficiency <10 ng/mL                                                                       | Vitamin D levels were significantly decreased in the patients with knee OA. Medial meniscal deterioration was seen in patients with low vitamin D levels, suggesting that vitamin D deficiency may play a role in the progression of medial compartment knee OA |
| Veronese et al   | Cross-sectional | 2756 patients were evaluated for OA pain                                         | Quintile 1: ≤53 nmol/L                                                                                | For the knee, low vitamin D levels were associated with the presence of OA. Cumulatively, in all women, the presence of pain in the sample as a whole, low 25-hydroxyvitamin D levels were positively correlated with the severity of OA and with OA-related pain, particularly when the hand and hip are involved |
| Jansen and Haddad| Cross-sectional | 139 elderly patients with advanced knee OA awaiting surgery had serum vitamin D levels measured | Vitamin D deficiency <40 nmol/L                                                                       | 24% of patients were found to have vitamin D deficiency                                                                                  |
| Konstari et al   | Prospective  | 5274 Finnish patients who did not have knee or hip OA at baseline had serum vitamin D levels measured. Serum vitamin D levels were measured 10 years later | Quintile 1: ≤33 nmol/L                                                                                | Low serum vitamin D concentration did not predict increased incidence of knee and hip OA                                               |

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development and progression of OA in relation to articular cartilage.

VITAMIN D AND OSTEOARTHRITIS

The efficacy of vitamin D in treating or preventing OA is controversial (Table 1). Some authors have found that vitamin D deficiency increases the risk of patients’ developing OA. In a prospective study, Zhang et al found that individuals with similar characteristics who were deficient in vitamin D and who were assessed radiographically for OA had an increased risk for OA of the knee, as assessed by radiologists blinded to the study. In a cross-sectional study with age-matched controls, Heidari et al found a similar result; however, this applied only to patients younger than 60 years. In an uncontrolled cohort study, Goula et al found that a significant percentage of men and women who were vitamin D deficient had an increased prevalence of hip and knee arthritis based on radiologic assessment.

It has been shown that patients with OA have decreased vitamin D serum levels (Table 2). Bassiouni et al and Vero et al both found that serum 25(OH)D levels were significantly decreased in the patients with knee OA and noted that medial meniscal deterioration was seen in patients with low vitamin D levels. In a cross-sectional study, Jansen and Haddad showed that in elderly patients with advanced knee OA, there was a high prevalence of vitamin D deficiency. Interestingly, Konstari et al both found in a longitudinal cohort study that low serum 25(OH)D concentration did not predict increased incidence of knee and hip OA when looking at 5274 Finnish patients; however, their results can be questioned since patients who were considered to be vitamin D deficient were included with patients with normal vitamin D levels in the results.

In several imaging studies, vitamin D deficiency is associated with decreased cartilage thickness (Table 3). In an ultrasonographic study, Malas et al found that vitamin D deficiency significantly decreased femoral cartilage thickness in the severe deficiency group. The vitamin D sufficient levels were established and no vitamin D sufficiency levels were determined. In a double-blind, placebo-controlled trial, Arden et al found that women with vitamin D deficiency had a higher risk for hip OA, but the significant difference was found in women. Monthly treatment with oral vitamin D did not produce significant clinical or cartilage volume structural differences in vitamin D-deficient knee OA cases over time. Results did not support vitamin D supplementation. There was no significant difference in rate of joint space narrowing in the medial compartment of knees due to vitamin D supplementation.

| Authors               | Study Design | Sample                                                                 | Vitamin D Serum Level Measurements                                                                 | Finding                                                                 |
|-----------------------|--------------|----------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------|------------------------------------------------------------------------|
| Malas et al           | Prospective cohort         | 80 patients classified into 3 subgroups according to vitamin D levels were examined | Vitamin D deficiency <10 ng/mL, Vitamin D insufficiency = 10.1-20.0 ng/mL, Vitamin D sufficient >20 ng/mL, Vitamin D insufficiency <15 ng/mL, Vitamin D insufficiency = 15.1-30.0 ng/mL, Vitamin D sufficient >30 ng/mL | The severe deficiency group had thinner femoral cartilage thickness, and it was concluded low vitamin D levels affect OA. Men with vitamin D deficiencies were at higher risk for hip osteoarthritis. |
| Chaganti et al        | Cross-sectional          | 1104 men with hip osteoarthritis were followed over 4.6 years        | Vitamin D deficiency <10 ng/mL, Vitamin D insufficiency = 10.1-20.0 ng/mL, Vitamin D sufficient >20 ng/mL, Vitamin D insufficiency <15 ng/mL, Vitamin D insufficiency = 15.1-30.0 ng/mL, Vitamin D sufficient >30 ng/mL | Vitamin D deficiency significantly decreased femoral cartilage thickness negatively. |

| Authors               | Study Design | Sample                                                                 | Vitamin D Serum Level Measurements                                                                 | Finding                                                                 |
|-----------------------|--------------|----------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------|------------------------------------------------------------------------|
| Hussain et al         | Prospective cohort         | 9135 adults older than 40 years who were undergoing hip arthroplasty for OA | Quartile 1: < 41 nmol/L, Quartile 2: 42 and 54 nmol/L, Quartile 3: 55 and 69 nmol/L, Quartile 4: > 70 nmol/L | Increasing serum vitamin D levels was associated with increased risk of hip arthroplasty in men. No significant difference was found. |
| Jin et al             | Randomized controlled trial | 413 patients with low vitamin D serum levels (12.5-60 nmol/L) were enrolled in the study. A total of 209 patients received oral vitamin D3 (50,000 IU) and 204 patients received identical placebos | No vitamin D sufficiency levels were established | Monthly treatment with oral vitamin D did not produce significant clinical or cartilage volume structural differences in vitamin D-deficient knee OA cases over time. Results did not support vitamin D supplementation. |
| Arden et al           | Double-blind, randomized placebo-controlled trial | 474 patients aged older than 50 years with radiographically evident knee OA were given either 800 IU cholecalciferol daily or placebo | Vitamin D deficiency <10 ng/mL, Vitamin D insufficiency = 10.1-20.0 ng/mL, Vitamin D sufficient >20 ng/mL | There was no significant difference in rate of joint space narrowing in the medial compartment of knees due to vitamin D supplementation. |
thickness in women between 20 and 45 years of age. In another longitudinal cohort study performed in the United States, men with vitamin D deficiency had a 2-fold increased likelihood of radiographic hip OA compared with men showing normal levels of vitamin D.\(^{11}\)

While these studies seem promising, imaging studies looking at increased vitamin D serum levels as a way to decrease the risk for OA have been inconclusive (Table 4). Hussain et al\(^ {23}\) showed that increased vitamin D serum concentrations were associated with an increased risk of hip arthroplasty for men with OA; however, this was not demonstrated in women. A 2-year randomized controlled trial in which 413 participants were given monthly treatments with oral vitamin D showed that oral supplementation did not produce significant clinical or cartilage volume structural differences in patients who were previously vitamin D deficient.\(^ {25}\) In a double-blind, randomized placebo-controlled trial, Arden et al\(^ {4}\) also showed that there was no significant difference in the rate of joint space narrowing in the medial compartment of knees due to vitamin D supplementation.

Studies have shown conflicting results as to whether low vitamin D levels are correlated with OA-related pain in patients (Table 5). In a prospective study with 3874 Korean patients aged 65 years and older in whom serum 25-hydroxyvitamin D levels were measured and compared with knee radiographic OA and knee pain, serum vitamin D did not have a significant effect on pain in older adults. For the knee, low vitamin D levels were associated with the presence of OA. In women, low vitamin D levels were associated with the presence of OA and with OA-related pain, particularly when the hand and hip are involved.

Vitamin D may be more strongly associated with pain measured on a questionnaire than radiographic change according to a general estimating equation.

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**TABLE 5**

| Authors          | Study Design       | Sample                                                                 | Vitamin D Serum Level Measurements                                                                 | Findings                                                                 |
|------------------|--------------------|------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------|
| Lee et al\(^ {28}\) | Prospective cohort | 3874 Korean patients aged 65 years and older had serum vitamin D levels measured. Levels were compared with knee radiographic OA and knee pain. | - Vitamin D deficiency <20 ng/mL  
- Vitamin D insufficiency = 21-29 ng/mL  
- Vitamin D sufficient ≥30 ng/mL | Serum vitamin D did not have significant effect on pain in older adults |
| Veronese et al\(^ {49}\) | Cross-sectional    | 2756 patients were evaluated for OA pain                                | - Quintile 1: ≤53 nmol/L  
- Quintile 2: >53 and ≤79 nmol/L  
- Quintile 3: >79 and ≤103 nmol/L  
- Quintile 4: >103 and ≤143 nmol/L  
- Quintile 5 >143 nmol/L | For the knee, low vitamin D levels were associated with the presence of OA. In women, low vitamin D levels were associated with the presence of OA and with OA-related pain, particularly when the hand and hip are involved |
| Muraki et al\(^ {36}\) | Cross-sectional    | 787 participants in the Hertfordshire Cohort Study answered a questionnaire on knee pain and underwent radiographic knee examinations | - Low tertile: <35.5 nmol/L  
- Middle tertile: 35.5-51.5 nmol/L  
- High tertile: >51.5 nmol/L | Vitamin D may be more strongly associated with pain measured on a questionnaire than radiographic change according to a general estimating equation |

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**TABLE 6**

| Authors          | Study Design       | Sample                                                                 | Vitamin D Serum Level Measurements                                                                 | Findings                                                                 |
|------------------|--------------------|------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------|
| McAlindon et al\(^ {34}\) | Double-blind, randomized placebo-controlled clinical trial | 146 patients with knee OA received either placebo or oral cholecalciferol, 2000 IU/d with dose escalation to elevate serum levels to more than 36 ng/mL | No vitamin D sufficiency levels were established | Vitamin D supplementation for 2 years did not reduce knee pain in patients with symptomatic knee OA |
| Sanghi et al\(^ {45}\) | Double-blind, randomized placebo-controlled trial | 103 patients with knee OA with vitamin D deficiency were given oral vitamin D or placebo and patients were followed for 1 year | Vitamin D deficiency ≤50 nmol/L | There is a small but statistically significant clinical benefit to vitamin D treatment in patients with knee OA |

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symptomatic knee OA patients were given oral doses of cholecalciferol to raise serum levels of vitamin D, there was no reduction in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) knee pain scores. In a double-blind study with 103 knee OA patients, patients receiving vitamin D oral supplements had slightly less pain compared with those receiving placebo after 1 year follow-up; however, these patients were not as physically capable as their placebo counterparts.

CONCLUSION

Much research has been conducted concerning the effects of vitamin D on OA, but few studies have been done to investigate the effects of vitamin D on articular cartilage degeneration and regeneration specifically. Vitamin D–sufficient patients have a lower risk of developing OA, and vitamin D sufficiency and supplementation decrease articular cartilage degeneration radiographically. Some studies have investigated the effect of vitamin D on OA progression and pain management; however, while there is no general consensus on the effects of vitamin D on OA, some results seem promising. Vitamin D supplementation may be a safe method to treat and prevent OA, but future research is required to define the specific pathway and ultimate efficacy.

REFERENCES

1. Aiger T, Støve J. Collagens—major component of the physiological matrix, major target of cartilage degeneration, major tool in cartilage repair. Drug Deliv. 2003;55:1569-1593.
2. Amanatullah DF, Yamane S, Reddi AH. Distinct patterns of gene expression in the superficial, middle and deep zones of bovine articular cartilage. J Tissue Eng Regen Med. 2014;8:305-314.
3. Amir AR, Abramson SB. The role of nitric oxide in articular cartilage breakdown in osteoarthritis. Curr Opin Rheumatol. 1998;10:263-268.
4. Arden NK, Cro S, Sheard S, et al. The effect of vitamin D supplementation on knee osteoarthritis, the VIDEO study: a randomised controlled trial. Osteoarthritis Cartilage. 2016;24:1858-1866.
5. Aydelotte MB, Kuettner KE. Differences between sub-populations of cultured bovine articular chondrocytes: morphology and cartilage matrix production. Connect Tissue Res. 1988;18:205-222.
6. Bach FC, Rutten K, Hendriks K, et al. The paracrine feedback loop between vitamin D3 (1,25(OH)2D3) and PTHrP in prehypertrophic chondrocytes. J Cell Physiol. 2014;229:1999-2014.
7. Bahar-Shany K, Ravid A, Koren R. Upregulation of MMP-9 production on knee osteoarthritis, the VIDEO study: a randomised controlled trial. Osteoarthritis Cartilage. 2016;24:1858-1866.
8. Bank RA, Bayliss MT, Lafeber FP, Maroudas A, Tekoppele JM. Ageing and zonal variation in posttranslational modification of collagen in normal human articular cartilage. The age-related increase in non-enzymatic glycation affects biomechanical properties of cartilage. Biochem J. 1998;330(pt 1):345-351.
9. Bassiouni H, Aly H, Zaky K, Abaza N, Bardin T. Probing the relation between vitamin D deficiency and progression of medial femoral-tibial osteoarthritis of the knee. Ann Rheum Dis. 2015;74:368-369.
10. Buckwalter JA, Mankin HJ, Grodzinsky AJ. Articular cartilage and osteoarthritis. Instr Course Lect. 2005;54:465-480.
11. Chaganti RK, Perini N, Cawthon P, Dam TL, Nevitt MC, Lane NE. Association of 25-hydroxyvitamin D with prevalent osteoarthritis of the hip in elderly men: the osteoporotic fractures in men study. Arthritis Rheum. 2010;62:511-514.

12. Daniel C, Sartory NA, Zahn N, Radeke HH, Stein JM. Immune modulatory treatment of trinitrobenzene sulfonic acid colitis with calcitriol is associated with a change of a T helper (Th) 1/Th17 to a Th2 and regulatory T cell profile. J Pharmcol Exp Ther. 2008;324:23-33.
13. Dodge GR, Poole AR. Immunohistochemical detection and immunochemical analysis of type II collagen degradation in human normal, rheumatoid, and osteoarthritic articular cartilages and in explants of bovine articular cartilage cultured with interleukin 1. J Clin Invest. 1989;83:647-661.
14. Dougherty KA, Dilisio MF, Agrawal DK. Vitamin D and the immunomodulation of rotator cuff injury. J Inflamm. 2016;9:123-131.
15. Forrest KY, Stuhldreher WL. Prevalence and correlates of vitamin D deficiency in US adults. Nutr Res. 2011;31:48-54.
16. Golding MB, Goldring GR. Osteoarthritis. J Cell Physiol. 2007;213:626-634.
17. Goulia T, Kouskoutis A, Drosos G, et al. Vitamin D status in patients with knee or hip osteoarthritis in a Mediterranean country. J Orthop Traumatol. 2015;16:35-39.
18. Guillot X, Semerano L, Sidenberg-Kermanac’h N, Falgarone G, Boissier M. Vitamin D and inflammation. Joint Bone Spine. 2010;77:552-557.
19. Heidari B, Heidari P, Hajian-Tilaki K. Association between serum vitamin D deficiency and knee osteoarthritis. Int Orthop. 2011;35:1627-1631.
20. Hochberg MC, Altman RD, April KT, et al. American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. Arthritis Care Res (Hoboken). 2012;64:465-474.
21. Holick MF. Vitamin D deficiency. N Engl J Med. 2007;357:266-281.
22. Holick MF, Chen TC. Vitamin D deficiency: a worldwide problem with health consequences. Am J Clin Nutr. 2008;87:1080-1086.
23. Hussain SM, Daly RM, Wang Y, et al. Association between serum concentration of 25-hydroxyvitamin D and the risk of hip arthroplasty for osteoarthritis: result from a prospective cohort study. Osteoarthritis Cartilage. 2015;23:2134-2140.
24. Jansen JA, Haddad FS. High prevalence of vitamin D deficiency in elderly patients with advanced osteoarthritis scheduled for total knee replacement associated with poorer preoperative functional state. Ann R Coll Surg Engl. 2013;95:569-572.
25. Jin X, Jones G, Cicuttini F, et al. Effect of vitamin D supplementation on tabile cartilage volume and knee pain among patients with symptomatic knee osteoarthritis: a randomized clinical trial. JAMA. 2016;315:1005-1013.
26. Kempson GE, Muir H, Pollard C, Tuke M. The tensile properties of the cartilage of human femoral condyles related to the content of collagen and glycosaminoglycans. Biochim Biophys Acta. 1973;297:456-472.
27. Konstari S, Kaila-Kangas L, Jaaskelainen T, et al. Serum 25-hydroxyvitamin D and the risk of knee and hip osteoarthritis leading to hospitalization: a cohort study of 5274 Finns. Rheumatology (Oxford). 2014;53:1778-1782.
28. Lee A, Chan SK, Samy W, Chiu CH, Gin T. Effect of hypovitaminosis D on postoperative pain outcomes and short-term health-related quality of life after knee arthroplasty: a cohort study. Medicine (Baltimore). 2015;94:e1812.
29. Loeser RF. Pathogenesis of osteoarthritis. UpToDate. https://www.uptodate.com/contents/pathogenesis-of-osteoarthritis. Accessed January 20, 2016.
30. Mabey T, Honsawek A. Role of vitamin D in osteoarthritis: molecular, cellular, and clinical perspectives. Int J Endocrinol. 2015;2015:383918.
31. Malins FU, Kara M, Aktekin L, Ersöz M, Özçakar L. Does vitamin D affect femoral cartilage thickness? An ultrasonographic study. Clin Rheumatol. 2014;33:1331-1334.
32. Martin JA, Buckwalter JA. Aging, articular cartilage chondrocyte senescence and osteoarthritis. Biogerontology. 2002;3:257-264.
33. Martin JA, Buckwalter JA. The role of chondrocyte-matrix interactions in maintaining and repairing articular cartilage. Biochirhol. 2000;37:129-140.
34. McAllinon T, LaValley M, Schneider E, et al. Effect of vitamin D supplementation on progression of knee pain and cartilage volume loss in...
patients with symptomatic osteoarthritis: a randomized controlled trial. *JAMA.* 2013;309:155-162.

35. Mow VC, Ratcliffe A, Poole AR. Cartilage and diarthrodial joints as paradigms for hierarchical materials and structures. *Biomaterials.* 1992;13:67-97.

36. Muraki S, Dennison E, Jameson K, et al. Association of vitamin D status with knee pain and radiographic knee osteoarthritis. *Osteoarthritis Cartilage.* 2011;19:1301-1306.

37. Naggal S, Lu J, Boehm MF. Vitamin D analogs: mechanism of action and therapeutic applications. *Curr Med Chem.* 2001;8:1661-1679.

38. National Institutes of Health, Office of Dietary Supplements. *Vitamin D Fact Sheet for Consumers.* Washington, DC: National Institutes of Health; 2016.

39. Orfanidou T, Malizos KN, Varitimidis S, Tsezou A. 1,25-Dihydroxyvitamin D(3) and extracellular inorganic phosphate activate mitogen-activated protein kinase pathway through fibroblast growth factor 23 contributing to hypertrophy and mineralization in osteoarthritic chondrocytes. *Exp Biol Med.* 2012;237:241-253.

40. Pelletier JP, Martel-Pelletier J, Howell DS. Etiopathogenesis of osteoarthritis. In: Koopman WJ, ed. *Arthritis and Allied Conditions: A Textbook of Rheumatology.* 13th ed. Baltimore, MD: Williams & Wilkins; 1997:1969-1984.

41. Peyron JG. The epidemiology of osteoarthritis. In: Moskowitz RW, Howell DS, Goldber VM, Mankin HJ, eds. *Osteoarthritis. Diagnosis and Treatment.* Philadelphia, PA: WB Saunders; 1984:9-27.

42. Poole A, Guilak F, Abramson S. Etiopathogenesis of osteoarthritis. In: Moskowitz R, Altman R, Hochberg M, Buckwalter J, Goldberg M, eds. *Osteoarthritis: Diagnosis and Medical/Surgical Management.* 4th ed. Philadelphia, PA: Lippincott Williams & Williams; 2007:27-49.

43. Salinger E, Moore J. Perioperative indicators of hypocalcemia in total thyroidectomy: the role of vitamin D and parathyroid hormone. *Am J Surg.* 2013;206:876-881.

44. Sandell LJ, Aigner T. Articular cartilage and changes in arthritis. An introduction: cell biology of osteoarthritis. *Arthritis Res.* 2001;3:107-113.

45. Sanghi D, Mishra A, Sharma AC, et al. Does vitamin D improve osteoarthritis of the knee: a randomized controlled pilot trial. *Clin Orthop Relat Res.* 2013;471:3556-3562.

46. St-Arnaud R, Naja RP. Vitamin D metabolism, cartilage and bone fracture repair. *Mol Cell Endocrinol.* 2011;347:48-54.

47. Tetlow L, Woolley DE. Expression of vitamin D receptors and matrix metalloproteinases in osteoarthritic cartilage and human articular chondrocytes in vitro. *Osteoarthritis Cartilage.* 2001;9:423-431.

48. Tetlow LC, Smith SJ, Mawer EB, Woolley DE. Vitamin D receptors in the rheumatoid lesion: expression by chondrocytes, macrophages, and synoviocytes. *Ann Rheum Dis.* 1999;58:118-121.

49. Veronese N, Maggi S, Noale M, et al. Serum 25-hydroxyvitamin D and osteoarthritis in older people: the Progetto Veneto Anziani study. *Rejuvenation Res.* 2015;18:543-553.

50. Vincent TL, Watt FE. Osteoarthritis. *Medicine (Baltimore).* 2014;42:213-219.

51. Xia B, Chen D, Zhang J, Hu S, Jin H, Tong P. Osteoarthritis pathogenesis: a review of molecular mechanisms. *Calcif Tissue Int.* 2014;95:495-505.

52. Zhang FF, Driban JB, Lo GH, et al. Vitamin D deficiency is associated with progression of knee osteoarthritis. *J Nutr.* 2014;144:2002-2008.

53. Zhen G, Cao X. Targeting TGF\(\beta\) signaling in subchondral bone and articular cartilage homeostasis. *Trends Pharmacol Sci.* 2014;35:227-236.

54. Zhu Y, Mahon BD, Froicu M, Cantorna MT. Calcium and 1\(\alpha\),25-dihydroxyvitamin D3 target the TNF-\(\alpha\) pathway to suppress experimental inflammatory bowel disease. *Eur J Immunol.* 2005;35:217-224.