SJIF Impact Factor (2025): 8.688| ISI I.F. Value: 1.241| Journal DOI: 10.36713/epra2016 ISSN: 2455-7838(Online)
EPRA International Journal of Research and Development (IJRD)
Volume: 10 | Issue: 11 | November 2025 - Peer Reviewed Journal

NUTRACEUTICALS APPROACH TO CHRONIC OSTEOARTHRITIS: FROM MOLECULAR RESEARCH TO CLINICAL EVIDENCE

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ABSTRACT

Approximately 58 million persons worldwide suffer from osteoarthritis (OA), a degenerative inflammatory disease of the joint cartilage. Pain, stiffness, and a decreased range of motion in relation to the arthritic joints are its defining characteristics. Over time, these symptoms may increase the risk of diabetes mellitus, falls, fractures, and overweight/obesity. Despite the fact that the current guidelines for treating osteoarthritis (OA) recommend pharmacological treatment, which includes cyclooxygenase (COX)-2-specific drugs, opioids, and non-steroidal anti-inflammatory drugs (NSAIDs), as the gold standard for this condition, there has been a lot of interest in nutraceutical supplements because they contain a diverse class of molecules that have the potential to improve cartilage formation and reduce inflammation, oxidative stress, pain, and joint stiffness. This review's objective is to outline the possible use of nutraceuticals in OA, emphasizing the molecular mechanisms of action as well as any available efficacy and safety evidence.

KEYWORDS: *Nutraceuticals, Osteoarthritis, Hyaluronic Acid Vitamin C, And Vitamind.*

INTRODUCTION

Early symptoms of osteoarthritis (OA), a widespread and chronic degenerative joint disease, usually include pain and stiffness in the hands, knees, hips, and other joints (1). Pathological alterations such meniscal degeneration, bone spur formation, cartilage degradation, and moderate synovitis progressively deteriorate as the disease advances, perhaps resulting in joint deformities and limited mobility in later stages (2,3). This significantly impairs functioning and day-to-day living, and many patients eventually need joint replacement surgery. Independent of other determinants, cohort studies have shown that osteoarthritis in the knee considerably relates to disability and loss of job (4). In addition to being one of the most common chronic illnesses, OA contributes significantly to disability and high morbidity rates worldwide (5). OA currently affects more than 500 million people globally, posing a significant socioeconomic burden (6,7). Thus, immediate action is needed to lessen the burden of OA worldwide. Our thorough examination of the GBD 2021 database will improve knowledge of the worldwide burden of OA, evaluate existing preventative measures, and provide policymakers with important information about OA treatment and prevention. This will facilitate the effective use of scarce healthcare resources and the creation of creative OA management techniques. Prior research has used data from GBD 2019 or 2020 to investigate the burden of OA and its risk variables at different levels (8,9).These studies, however, mostly concentrate on evaluating OA in certain nations, anatomical locations, or risk factors.

Our work examines the prevalence, incidence, and DALYs of OA at the national, regional, and worldwide levels during the last 30 years using the GBD 2021 database in order to provide a comprehensive understanding of the current global burden of OA. In order to evaluate the distribution and shifts in the worldwide burden of OA, it also looks at trends by classifying nations and areas according to the SDI.

Risk Factors for Knee OA

The pathogenesis of knee OA is complex. It could be viewed as the final result of a cross-talk between systemic and local forces.

Growing Older

Growing older is identified as the primary risk factor for the development of OA because it is most prevalent among the elderly [15]. Changes in the tissues of the joints brought on by aging make the joint more vulnerable to the onset and advancement of OA throughout time. Increased susceptibility to degeneration results from changes in the mechanical properties of cartilage caused by extracellular matrix (ECM) rearrangement, AGE accumulation, decreased aggrecan size, decreased hydration, and increased collagen cleavage [16].Meanwhile, in chondrocytes, mitochondrial abnormalities, oxidative stress, and diminished autophagy alter their capacity, stimulating the catabolic pathway and cell death [17].

Joint Injury and Trauma

Articular cartilage is a durable tissue, capable of enduring the repetitive stress produced from the daily physical activities. However, it remains susceptible to trauma that can damage the cartilage and subchondral bone. Such damage, along with intra-articular fracture, can increase the risk of OA progression [18]. The pathologic changes are frequently evident within 10 years after injury, with the time of beginning affected to some extent by the patient's age at the time of injury [19].The OA process is triggered by the breakdown of collagen and proteoglycan following joint traumas, as well as the presence of increased host inflammatory mediators, such as interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-α) [20].

Being Overweight

OA is impacted by obesity both directly and indirectly. Obese patients' elevated body mass index (BMI) indicates increased body weight, which causes severe overloading and damage to the weight-bearing joint [21].Furthermore, adipocytes in adipose tissue produce leptin and adiponectin, which are metabolic abnormalities linked to elevated BMI. These abnormalities have been linked to direct effects on joint tissues that facilitate the development of osteoarthritis. The proinflammatory state during OA has been linked to the production of proinflammatory cytokines by macrophages, specifically TNF-α and IL-6 [22].

The Netherlands Epidemiology of Obesity study demonstrated the two paradigms of the association between elevated BMI and OA: knee OA was linked to weight and fat-free mass after controlling for metabolic factors, while hand OA was linked to the metabolic syndrome after controlling for weight [23].

Genetics

According to twin epidemiological research, hereditary variables account for 39–65% of OA cases in the general population [24]. Certain rare mutations in type II, IX, or XI collagen—common collagens present in articular cartilage—create hereditary forms of OA, which can start as early as puberty and induce a severe, debilitating form of arthritis that affects several joints [25]. However, compared to OA of the hands, the data linking hereditary variables to OA of the lower extremity joints, including the knee or hip, is less clear [26].

Anatomical Elements

The development of OA may be influenced by the joint's form. Lower extremity alignment has been found to be a key anatomic feature associated with knee OA. Furthermore, a leg length difference of ≥1 cm, varus and valgus deformities, and cruciate ligament tearing are additional factors that can raise the risk for the development and progression of OA in the knee [10]. Tibiofemoral OA is more likely to occur in people who have either valgus alignment or varus alignment (bow-legged) [27]. Changes in joint mechanics as the initial etiology of OA provide the best explanation of the link between anatomic variables and OA. The mechanotransduction pathways that lead to increased production of inflammatory mediators and proteolytic enzymes are initiated by altered mechanics that exert excessive and abnormal demands on joint tissue cells [28]. The occurrence of ankle OA caused by anatomic causes is rare, as evidenced by the recent rise in ankle OA diagnoses. Almost always, a previous fracture is the cause of ankle OA [29]. The lack of reporting on ankle OA may be the cause of this observation.

The Demographics

OA is more likely to develop in women. Women over 65 have a 68% incidence rate of OA, but males over 65 have a 58% incidence rate. The high prevalence of OA in the postmenopausal years may be explained by the disease's significant age correlation. Because postmenopausal women have higher levels of calcitonin and bone resorption, they are more prone to knee arthritis. Nonetheless, there is some data that suggests estrogen depletion may have a role [30]

Ethnicity and OA are known to be associated. Compared to other ethnic groups like African Americans, Chinese, and Hispanics, Caucasians in the US showed a lower frequency of OA [31]. The variations in bone resorption among ethnic groups, which are regularly documented in epidemiological investigations of bone health, could be a contributing factor in these discrepancies [32]. The discovery of certain radiographic variations in certain osteoarthritis characteristics based on ethnicity [33] lends credence to this. On the other hand, it has also been hypothesized that the socioeconomic and cultural practices of a particular ethnic group influence the variation in OA prevalence [34].

Axis of the Gut-Joint

When quantitative and qualitative changes to the gut microbiota (GM) revealed a persistent, low-grade, and chronic systemic inflammation that later appeared in OA, the link between gut dysbiosis and OA was established [35]. When left undisturbed, the GM carries out a number of tasks, including absorbing nutrients, preserving metabolic homeostasis, warding off infections, and building mucosal and systemic immunity. When the GM was disturbed in gut dysbiosis, the host's metabolism and immunological response were also affected. The pathophysiology of OA was made worse by these disturbances taken together.

Adverse Alterations in OA

Given its complexity, a wide range of factors influence the onset, course, and severity of OA. Moreover, the rate at which OA advances varies from person to person. There has been evidence of a negative correlation between articular cartilage deterioration and subchondral bone alterations at the cartilage–bone junction. A higher grade of cartilage degradation is seen as the subchondral bone thickens [36]. The articular cartilage surface frequently exhibits the earliest pathological alterations in OA, with fibrillation developing in focused areas that are under the most strain. The loss of matrix causes a sharp increase in the proliferation of chondrocytes, the sole cell type found in cartilage. Certain chondrocytes shift phenotypically to become hypertrophic chondrocytes, which resemble the cells in the hypertrophic zones of the growth plate. Due to the ongoing synthesis of proteases triggered by proinflammatory cytokines, which in turn cause chondrocytes to create more cytokines and proteases in an autocrine and paracrine way, significant matrix breakdown and loss occur as OA worsens. Areas of the matrix devoid of cells due to chondrocyte apoptosis can be observed as substantial matrix damage occurs.Subchondral sclerosis, which is brought on by an increase in collagen production, osteophyte formation, and bone cysts at more advanced stages are among the bone abnormalities associated with OA. Osteophytes have been defined as cartilage and bone growths that form at the joint site. With the exception of the lateral tibia and medial patella, the size and local cartilage constriction affect the direction of osteophyte formation [37]. Osteophyte development is supported by biomechanical variables. The majority of OA patients have hypertrophy and inflammation of the synovium [38]. Although it does not cause primary OA, synovitis inflammation does contribute to the development of pain and illness [39].Since plain radiographs only show a portion of OA, such as bone alterations that lead to subchondral sclerosis, cysts, and osteophyte formation, and cartilage loss that narrows joint spaces, they understate the involvement of joint tissue in the disease. By the time radiographs show these alterations, the disease has progressed considerably [40].

In addition to detecting early disease, magnetic resonance imaging (MRI) investigations have demonstrated degenerative changes in soft-tissue structures outside of cartilage, such as ligaments and the menisci of the knee, as well as matrix alterations in cartilage, synovitis, and bone marrow lesions [41].When a patient has established knee arthritis and their symptoms are out of proportion to radiographic results, or when they have unexplained knee pain and swelling, the arthroscope can be a valuable diagnostic tool [42].Furthermore, the paradigm has changed to emphasize the role of different inflammatory mediators, proteinases, cell proliferation, and biochemical markers in the development of the disease, in addition to the pathological alterations already described.

Mediators of Inflammation

The Chemokines and Cytokines

The main ingredient in the majority of inflammatory processes are inflammatory mediators like cytokines. As a result, the pathophysiology of OA has been linked to several cytokines. Proinflammatory cytokines and chemokines disturb cartilage matrix homeostasis in OA patients [43,44]. IL-1, IL-6, and IL-8 were found to be upregulated when the cytokines and chemokines implicated in the pathogenesis of OA were investigated [45,46,47].

In order to promote the joint synthesis of proteases, nitric oxide (NO), and eicosanoids such prostaglandins and leukotrienes by macrophages and chondrocytes, these cytokines function as both autocrine and paracrine agents. The activity of these inflammatory mediators in the cartilage then causes matrix production to be inhibited, cellular death to be promoted, and catabolic pathways to be triggered [47].The proinflammatory cytokines' suppression of autophagy is what triggers cellular death, especially in chondrocytes [48,49].

The activated chondrocytes' generation of IL-1 then triggers the synthesis of MMPs, specifically MMP-1, MMP-3, and MMP-13. Proinflammatory cytokines including TNF-α, IL-6, and the chemokine IL-8 are also amplified in conjunction with this, amplifying the effects of cartilage matrix breakdown in the catabolic cascade and accelerating the demise of articular chondrocytes [45,50]. By preventing the synthesis of important ECM constituents such proteoglycans, aggrecan, and type II collagen, IL-1 has also been shown to have a role in the deterioration of cartilage matrix [51,52,53]. Furthermore, when fibronectin fragments cause chondrocytes to release inflammatory cytokines, chemokines, and MMPs, it is evident that the protein is involved in the breakdown of cartilage [54,55]. Chondrocytes in healthy adult cartilage produce matrix constituents at a relatively sluggish rate. Lastly, the other main factor influencing the onset and advancement of OA is chondrocyte senescence. This results from the senescent cells' diminished ability to preserve and repair the extracellular matrix of cartilage [56]. The senescence-associated secretory phenotype, which is also known to be released by senescent cells, includes the important cytokines IL-6 and IL-8, respectively [57].

The proteases

The homeostasis of articular cartilage is significantly influenced by the MMP family. The collagenous framework is broken down by collagenases (MMP-1, MMP-13), whereas stromelysin (MMP-3) and aggrecanase (ADAMT-4), which break down proteoglycan, are key players in the breakdown of extracellular matrix (ECM) [44,58]. OA chondrocytes produce inflammatory cytokines, such as TNF-α and IL-1, which can block MMP enzyme inhibitors, boost MMP expression, and reduce the formation of extracellular matrix. Collagenases 1, 2, and 3 (MMP-1, MMP-8, and MMP-13, respectively) involved in type II collagen degradation are activated by active stromelysin [51,52,53].Given that type II collagen is the predominant collagen type in extracellular matrix, MMP-13, the protease that preferentially breaks down type II collagen, may be the most significant factor in the development of OA. MMP-13 expression is, in fact, significantly elevated in OA [47,59]. MMP-13 plays a significant role in the deterioration of human articular cartilage throughout OA, as evidenced by its high expression in OA cartilage as opposed to MMP-1 and MMP-3, which are seen in high concentrations in OA synovial fluid [58,59,60]. Furthermore, the genes that encode MMP-13 are only expressed by hypertrophic chondrocytes, and they are all found in OA cartilage [55]. The integrity of articular joint tissue is determined by the balance between the anabolic and catabolic processes, which is regulated by cytokines. Anabolic activity predominates over catabolic activity throughout pathogenesis, leading to tissue deterioration [61].

Nutraceuticals for OA Management and Prevention of Worsening

Acid Hyaluronic

Repeated monomers of β-1,4-D-glucuronic acid and β-1,3-N-acetylglucosamine combine to form hyaluronic acid (HA), a mucopolysaccharide. With its exceptional viscoelasticity, high moisture retention capacity, high biocompatibility, and hygroscopic qualities, this molecule is especially prevalent in synovial fluid and serves as a lubricant, shock absorber, joint structure stabilizer, and regulator of water balance and flow resistance [94]. For patients with knee or

hip OA, HA is the recommended course of treatment. It acts more slowly than steroid therapies, but its effects can continue for a lot longer [95]. HA injections must be given frequently into the joint cavity, despite the fact that they have demonstrated significant benefits in reducing the clinical symptoms of OA patients [96]. The requirement for several HA injections is a significant disadvantage of the treatment due to the inconvenience of frequent clinic visits and the proportionate rise in side effects with the number of injections. For these reasons, oral administration is a better option for relieving OA symptoms when taking into account the drawbacks of HA injection [97].

Action Mechanism

The first HA mechanism of action that has been suggested relates to chondroprotection. It has been demonstrated that HA increases chondrocyte proliferation while decreasing apoptosis [98]. By binding to cluster of differentiation 44 (CD44) receptors, HA inhibits the expression of interleukin (IL)-1β and reduces the production of matrix metalloproteinase (MMP)−1, 2, 3, 9, and 13 [99]. In addition to binding to CD44, HA also binds to the receptor for hyaluronan-mediated motility (RHAMM), which is believed to help in chondroprotection [92]. Furthermore, by CD44 binding, it may decrease MMP-13 and IL-6, which could impact the subchondral bone [100]. One important aspect in the impact on OA subchondral bone has been proposed to be the reduction of MMP-13 expression [93].The therapeutic effects of HA on OA may not necessarily necessitate its absorption, despite human studies showing that oral supplementation with this molecule can reach the blood and be transported to the skin and joints [101]. In fact, HA may bind to the intestinal toll-like receptor 4 (TLR4) and carry out its biological actions by secreting more suppressor of cytokine signaling 3 (SOCS3), which in turn suppresses the release of pro-inflammatory cytokines [102]. In this context, it has been noted that HA suppresses the pro-inflammatory mediators TNFα, PGE2, IL-8, and IL-6 [103]. Furthermore, the pro-inflammatory protein pleiotrophin is suppressed when HA binds to TLR4 [102]. In this context, it has been noted that HA suppresses the pro-inflammatory mediators TNFα, PGE2, IL-8, and IL-6 [103]. Furthermore, the pro-inflammatory protein pleiotrophin is suppressed when HA binds to TLR4 [102]. Additionally, HA inhibits NF-kB by binding to the intercellular adhesion molecule (ICAM-1), which lowers IL-6 production [104]. N-acetyl glucosamine, the monosaccharide that makes up HA together with D-glucuronic acid, is another potential method of action. Lysosomal enzymes in cells transform N-acetyl glucosamine into glucosamine, enabling the chondroprotective and anti-inflammatory properties of glucosamine as detailed in the corresponding paragraph [105]. Proteoglycan production, including aggrecan, was promoted by HA therapy, slowing the course of OA [106].Because of its mechanical function, HA helps lubricate the joint capsule and reduce friction, hence preventing degeneration. In order to prevent chondrocyte tissue from degrading, HA acts as a cushion to absorb pressure and vibration [107].

By reducing the mechanical sensitivity of stretch-activated ion channels, HA effectively inhibits the pain response and has analgesic benefits. Additionally, HA lessens the pain response seen by joint-sensitized nociceptors, whose activity is influenced by the HA concentration [108].

Safety and Effectiveness

The outcomes of animal studies employing radiolabeled HA unequivocally showed that oral HA would, in fact, be absorbed, distributed, and stored for extended periods of time in the

skin, bone, and synovial joints [109]. Human RCTs supported these conclusions by demonstrating that oral supplementation with this molecule can preserve its biological activity by reaching the circulation and distributing it to the skin and joints [101].The symptoms of knee OA may be lessened by taking HA orally, according to several studies [110,111]. Sato et al. showed that a 12-week course of 240 mg/day of HA was linked to a significant improvement in the Japan Orthopaedic Association (JOA) score and the Japanese Knee Osteoarthritis Measure (JKOM) score when compared to baseline values [112]. When OA patients were given 200 mg of HA daily for eight weeks, their WOMAC ratings improved in comparison to the placebo group [108]. Following an 8-week course of 200 mg of HA supplementation, Iwaso et al. reported similar outcomes, highlighting improvements in both WOMAC and JKOM scores [113].60 osteoarthritic participants (Kellgren-Lawrence grade 2 or 3) were randomized to receive either HA (200 mg/day) or a placebo in a one-year RCT. The subscale for "pain and stiffness" showed the greatest improvement at the conclusion of treatment, and patients who combined therapeutic activities with HA therapy showed the greatest recovery [114].Before drawing any conclusions, it is important to discuss a number of limitations, even if various research indicate that oral HA supplementation has good effects on OA. In actuality, the results may be impacted by the various types of supplemented hyaluronic acid (which were frequently not mentioned in the studies), the short study periods, the small sample size, and the absence of suitable controls. New long-term RCTs with standardized HA are desperately needed to shed light on these problems, and it would be ideal to suggest such a nutraceutical in clinical practice.

Humans can safely take oral supplements of HA at up to 200 mg per day for up to 12 months, according to validated research [109]. Medium-term (3–6 months) supplementation periods were used in a number of safety investigations, and safety was verified [115].

Vitamin C

Szent-Gyorgyi isolated vitamin C, also known as ascorbic acid, for the first time in 1923, and Howarth and Hirst synthesized it. Citrus fruits, red and green peppers, tomatoes, strawberries, broccoli, Brussels sprouts, turnips, and other leafy vegetables are particularly high in it. Because of its reactivity with a variety of aqueous free radicals and ROS, it is a water-soluble molecule with potent antioxidant qualities [116].Scurvy, anemia, capillary hemorrhage, muscular degeneration, infections, bleeding gums, poor wound healing, atherosclerotic plaques, and neurotic disorders are among the ailments that can be linked to a lack of this molecule. Furthermore, several studies have shown that vitamin C intake appears to be linked to a lower incidence of OA and cartilage loss in people, most likely due to a decrease in oxidative stress [117,118]. Although the European Food Safety Authority (EFSA) has accepted a claim for vitamin C's function in normal collagen synthesis, it is still unclear if this supplement has any further impact on preventing the advancement of osteoarthritis.

Action Mechanism

A common antioxidant and antiradical supplement is vitamin C. Since it is readily interconvertible and physiologically active in both its reduced (ascorbate) and oxidized forms as dehydroascorbic acid, it serves as a significant antioxidant. The ascorbyl radical, a rather poor reactive intermediate that disproportionately produces ascorbate and dehydroascorbate, is the result of ascorbic acid's direct reaction with free radicals going through single-electron oxidation. In this regard, ascorbic acid can decrease organic (RO2) and nitrogen (NO2•) oxy

radicals, as well as the harmful ROS superoxide anion (O2•) and hydroxyl radical (OH•). Furthermore, by preventing the oxidation of other vitamins, like A and E, this molecule may potentially have an indirect effect.Given this, ROS-induced damage has long been regarded as harmful and plays a significant part in the development of OA by inducing cytotoxicity and cellular damage [8]. Pro-inflammatory mediators have a crucial part in the pathophysiology of OA, despite the fact that it is categorized as a "non-inflammatory arthropathy" [119]. Additionally, vitamin C is a sulphate carrier in the synthesis of glycosaminoglycan [121] and an electron donor in the synthesis of type II collagen [120]. Additionally, ascorbic acid keeps the active center of metal ions in a reduced state for the best activity of the enzymes hydroxylase and oxygenase, and it is a co-factor for the hydroxylation and activity of mono-oxygenase enzymes in the manufacture of collagen, carnitine, and neurotransmitters [109]. One of the most significant manifestations of OA, frequently linked to cartilage degeneration, is the reduction of the articular cartilage's extracellular matrix of sulphated proteoglycans [117]. Hence, vitamin C insufficiency may be regarded as a risk factor for the development of OA, and its supplementation in primary prevention may offer a potential remedy for OA, particularly when combined with traditional or non-traditional therapy.

Safety and Effectiveness

In addition to its well-known antioxidative properties, vitamin C has several other properties that can help prevent the progression of OA, such as regulating apoptotic processes (via the development of procaspase-3, procaspase-9, and Bax) and pro-inflammatory cytokines and MMPs. It was demonstrated that administering 100 µM vitamin C to an in vitro chondrosarcoma cell line (SW1353) prevented the oxidative stress, apoptosis, and loss of proteoglycans that were brought on by administering 5 µM monosodium iodoacetate (MIA). Additionally, the pro-inflammatory cytokines MMP-1, MMP-3, and MMP-13 as well as IL-6, IL-17A, and TNF-α were not expressed [122]. In vivo monosodium iodoacetate (MIA)-induced OA animals (supplemented with 100 mg/kg of vitamin C) showed comparable outcomes [118]. Numerous in vivo studies have shown that vitamin C's ability to fend off oxidative stress may reduce the risk of osteoarthritis development and cartilage degradation in humans [113,117]. Nevertheless, some research suggested that there was no connection between incidence radiographic knee OA and circulating vitamin C levels [123].Those without baseline knee OA who self-reported taking vitamin C supplements had an 11% lower chance of developing knee OA than those who self-reported not taking any vitamin C supplements (risk ratio (RR)=0.89, 95% CI 0.85, 0.93), according to a prospective cohort study of 1023 participants. Furthermore, it was shown that vitamin C supplementation may be helpful in reducing incident knee OA in patients having radiographic knee OA at baseline, if confounding variables were taken into account [124]. Radiographic knee OA was found to be significantly correlated with vitamin C intake but not with dietary carotenoids, vitamin E, or selenium in a cross-sectional analysis of 4685 participants that examined the relationships between these antioxidants and radiographic knee OA [117]. Additionally, the lipoperoxides associated with hip bone loss were considerably reduced by vitamin C use ($p < 0.05$ when compared to the placebo group) [125]. By likely serving as a cofactor for the enzyme peptidyl glycine α-amidating mono-oxygenase (PAM), which is involved in the synthesis of endomorphin-1, vitamin C may help improve quality of life and decrease the need for painkillers [30,126].The use of a straightforward, affordable, and widely accessible

supplement to potentially lessen the impact of OA is worth further research given the disease's enormous economic cost. However, before making any final decisions, long-term RCTs are desperately needed.

In certain patient populations, vitamin C seems to be a safe and useful supplementary treatment for both acute and chronic pain alleviation [125]. Further research is necessary to ascertain the best route of administration, the ideal dose and frequency of administration, the possible mechanisms of action of this molecule in OA disease, and the baseline and post-intervention vitamin C concentrations to see if particular patient groups respond.

Vitamin D

The Institute of Medicine (IOM) recommended vitamin D in 2011 for bone health since it is a well-known lipophilic molecule that improves calcium absorption, bone mineral density, and vitamin D deficient rickets/osteomalacia [127]. Vitamin D deficiency affects 20% of people in northern Europe, 30% to 60% of people in western, southern, and eastern Europe, and up to 80% of people in Middle Eastern countries, despite the fact that it can be acquired through foods like mushrooms, fatty fish, and vitamin D-fortified products as well as through the cutaneous synthesis in response to UV-B exposure. More than 10% of Europeans have a severe deficiency (serum 25(OH)D< 30 nmol/L or 12 ng/mL) [128].The potential impact of vitamin D on the development and course of OA has been the subject of numerous investigations. Accordingly, the fact that vitamin D receptors (VDRs) are expressed in the articular cartilage of OA patients but not in that of healthy volunteers may suggest that this hormone directly affects the possibility of articular cartilage degradation [129,130]. Furthermore, vitamin D may indirectly affect OA by way of the endocrine system.

Action Mechanism

A key immunoregulator of inflammation, vitamin D affects how white blood cells (macrophages, dendritic cells, T and B lymphocytes) react [131]. Activation of VDR localized on white cell membranes, in particular, also encourages the blocking of transcription of cytokine genes, including NF-AT (nuclear factor of activated T cells) and NF-κB, which lowers the production of TNF-α and IL-1, which are thought to be inflammatory pathways for cartilage degradation [129]. Furthermore, a number of investigations have demonstrated that injured cartilage exhibits an upregulation of VDRs. VDR is overexpressed in regions where late-stage rheumatoid arthritis cells are eroding, according to an in vitro research [129]. Both Orfanidou et al. [132] and the same research team [131] verified this outcome in people.VDR overexpression appears to trigger a signaling cascade that increases chondrocyte synthesis of MMPs 1, 3, and 9, which leads to the deterioration of bone and cartilage [133]. Additionally, vitamin D interacts with osteoblast-expressed VDRs. In comparison to healthy and osteoporotic cells, OA osteoblasts expressed a considerably decreased receptor activator of NF-κ B ligand (RANKL)/osteoprotegerin (OPG) ratio, according to a research by Corrado et al. [134]. Osteoclastogenesis and consequently bone resorption are regulated by RANKL and its decoy receptor OPG. Furthermore, OA osteoblasts expressed OPG at a much higher level than both controls and osteoporosis patients. These findings, however, were in contrast to those of Giner et al., who discovered that osteoporotic osteoblasts secreted more OPG than OA [135]. An significant mechanism in the pathophysiology of OA is the angiogenesis process, which may be regulated by vitamin D. Indeed, investigations in vitro have shown that 1α,25(OH)2D3 regulates the expression of vascular endothelial growth factor (VEGF), including osteoarthritic osteoblasts [136]. This bolsters the hypothesis that osteoblasts may control angiogenesis in subchondral bone and may associate vitamin D with the onset and course of osteoarthritis.

A small body of research indicates that vitamin D increases bone resorption via indirectly influencing osteoclasts by activating the RANKL signaling described above [137]. Finally, the transforming growth factor-beta (TGF-β)/SMAD pathway implicated in OA may also be regulated by vitamin D [133]. TGF-β protects healthy joints by suppressing the production of MMP13 [138]. Accordingly, the healing responses in the joint and cartilage injury are altered when TGF-β is blocked, since its expression declines with age [139]. In contrast to these findings, TGF-β appears to exacerbate OA in OA joints. It has been demonstrated that OA in the mesenchymal stem cells of subchondral bone is attenuated by TGF-β signaling suppression [140].These findings suggest that TGF-β may prevent OA in healthy joints, even though it may make pre-existing OA joints worse. However, vitamin D should be advised, particularly for older adults with OA who have low plasmatic levels of this hormone (<30 ng/mL) linked to comorbidities like heart disease and bone health issues. Indeed, it has been shown to improve quality of life, decrease discomfort (VAS), lessen oxidative protein damage, and enhance physical performance and grip strength in these patients [141].

Safety and Effectiveness

There is conflicting evidence about whether vitamin D insufficiency raises the risk of developing OA. Relatively high (≥50 nmol/L) vitamin D status has not been linked to the onset of OA as manifested by pain, radiologic OA, or cartilage volume loss, according to a number of observational studies [142,143,144,145]. In an Irish study of outpatients with rheumatology, 26% had severe vitamin D deficiency (<12 ng/mL) and 70% had vitamin D deficiency (<21 ng/mL) [146]. Accordingly, 62% of OA patients had hypovitaminosis D, and radiographic hip OA has also been linked to low vitamin D status [147].A systematic review by Cao and colleagues [151], which included 15 studies, found strong evidence for an association between 25(OH)D3 and cartilage loss in knee joints and moderate evidence to support a positive association between low levels of vitamin D and radiographic knee OA. Similar findings were reached by osteoporotic fractures in a study of men in which vitamin D insufficiency or deficiency status were associated with a doubled risk of hip OA [148]. The Tasmanian Older Adult Cohort Study also found an inverse correlation between time spent in the sun and the loss of knee cartilage [143].The research team of Konstari and associates, however, found no link between vitamin D levels and the likelihood of getting osteoarthritis in the knees of Scandinavians [152,153]. In two longitudinal investigations (1203 persons), Felson et al. did not find a correlation between low vitamin D and the structural deterioration of afflicted joints (cartilage loss by magnetic resonance imaging and joint space narrowing by radiography) [145].

A five-year change in knee and hip pain was predicted for those with baseline plasma vitamin D deficits (12.5–25 nmol/L) [154]. However, in individuals with hypovitaminosis D, increased vitamin D level may reduce joint discomfort and perhaps radiologic OA [155,156].There are currently insufficient or conflicting research on the possible link between vitamin D level and the development of radiologic OA or cartilage volume loss in individuals with "suboptimal" 25(OH)D. Cholecalciferol supplementation in individuals with symptomatic knee OA did not differ from the placebo group in terms of cartilage degradation or WOMAC knee pain levels in a 2-year RCT [156]. Although there was a strong correlation between vitamin D and knee pain, 787 participants in the cross-sectional Hertfordshire

Cohort Study did not exhibit any association between radiographic knee OA and vitamin D status [157]. Additionally, an RCT involving 103 individuals with osteoarthritis in their knees who received oral vitamin D supplements (60,000 IU/day for 10 days and 60,000 IU/month for 12 months) revealed a slight but significant relationship between the functional scores and the level of pain (compared to the placebo group) [32].

Vitamin D levels have been demonstrated to predict the outcomes of osteoarthritis (OA) in patients receiving total hip replacement. Additionally, there appears to be a favorable link between plasma 25(OH)D3 levels and preoperative and postoperative Harris hip scores [158].In summary, there is inconsistent evidence regarding the impact of low vitamin D levels on the functional features of knee OA. According to studies conducted in vitro that examined the hormone's molecular mechanisms of action, vitamin D appears to have detrimental effects on the health of OA cartilage; yet, other human studies suggested that it may also play a role in preventing pain, radiologic OA, and cartilage volume loss. In this regard, it is imperative to conduct extensive longitudinal, multicentric research with people of varied skin pigmentations, nations, and ethnicities in order to completely ascertain the connection between vitamin D supplementation and the onset or progression of OA.Furthermore, extensive meta-analyses will assist clarify any connections between low vitamin D and OA and provide more compelling interpretations of the current data. Supplementing with vitamin D is generally safe and well-tolerated. A number of variables, including vitamin D plasmatic levels, administration dose and regimen, results, and potential influences from age and sex, may affect the upper limit of vitamin D dose safety. However, taking 1000–2000 IU of vitamin D per day is thought to be safe for preventing or treating vitamin D deficiency or insufficiency [159].

CONCLUSIONS

In conclusion, when used in conjunction with traditional therapy, nutraceuticals may be a viable approach to managing OA. To focus attention on the molecular mechanisms of nutraceuticals in mitigating OA processes and pain, the potential combination of anti-OA molecules with pain relief nutraceuticals, and the long-term safety and efficacy of these treatments, larger and longer studies are urgently needed to definitively consider this unconventional approach in clinical practice.

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