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Major clinical outcomes and nutrological treatments of knee osteoarthritis: a systematic review

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Abstract

Introduction: Osteoarthritis (OA) is the most prevalent joint disease and is considered the rheumatic condition with the greatest socioeconomic consequences, especially knee osteoarthritis, as it hinders mobility. Currently, there is no cure for OA; therefore, available treatments aim to reduce symptoms such as pain and inflammation, maintain joint mobility, and limit loss of function. Because OA has a known inflammatory component, nutrition is believed to play a vital role in the prevention and ongoing management of OA. **Objective:** This article aims to analyze the available evidence on the prevention and treatment of knee OA, including dietary interventions that may play a potential role in disease management. **Methods:** The systematic review guidelines of the PRISMA Platform were followed. The search was conducted from January to March 2025 across Scopus, Embase, PubMed, ScienceDirect, Scielo, and Google Scholar databases. Study quality was assessed using the GRADE tool, and risk of bias was analyzed using the Cochrane tool. **Results and Conclusion:** 154 articles were recruited for the initial assessment. A total of 58 articles were evaluated, and 29 were included in this systematic review. Using the Cochrane risk of bias tool, the overall assessment resulted in 42 studies with a high risk of bias and 24 studies that did not meet the GRADE criteria. Most studies presented homogeneous results, with X^2 =69.7% > 50%. The results showed that some nutrients, vitamins, and antioxidants are widely discussed in the literature for the treatment and prevention of the disease. Free radical management is necessary, and the influence of nutrients and diet on cartilage metabolism and OA may represent a long-term adjuvant alternative in the treatment of patients with knee OA. The effects of dietary modifications on lipid and cholesterol profiles, adequate vitamin levels, and weight reduction in obese patients may influence the course of the disease.

Keywords: Osteoarthritis. Knee. Nutritional approach. Prevention. Treatment.

Introduction

Osteoarthritis (OA) is the most prevalent joint disease and is considered the rheumatic condition with the greatest socioeconomic consequences, especially knee osteoarthritis, as it impairs mobility. The incidence of the disease increases with age, progressing over decades until loss of joint function occurs. Furthermore, elderly patients have several comorbid conditions that increase the complexity of treatment [1,2].

To date, there is no cure for OA, therefore, available treatments aim to reduce symptoms such as pain and inflammation, maintain joint mobility, and limit loss of function. Several international guidelines have been published with recommendations for the management of knee osteoarthritis, and all guidelines include both non-pharmacological and pharmacological

approaches. Non-pharmacological interventions include weight reduction, adequate physical activity, physical therapy, muscle strengthening, mobility aids, knee braces, footwear, and insoles, electrical stimulation, and acupuncture, in addition to pharmacological treatments **[2,3]**.

There is a great need for OA prevention. The first step should be a healthy lifestyle, weight loss, and nutrition with specific nutrients that can help achieve this goal. Furthermore, several foods can help prevent or treat OA, using them as adjuncts to treatment. Several emerging alternatives exist, and it is increasingly recognized that nutritional strategies can help maintain bone and joint health **[2-4]**.

The pathophysiology of OA is now recognized to involve much more than simple mechanical wear and tear of articular cartilage. It involves a complex interplay between pro-anti-inflammatory joint mediators, as well as anabolic versus catabolic signaling in chondrocytes, cartilage matrix, synovium, and synovial fluid. Pro-inflammatory cytokines, in addition to local and systemic factors such as oxidative stress due to decreased joint antioxidant capacity, play important roles in the pathobiology of OA and cartilage metabolism **[3,5,6]**.

Because OA has a known inflammatory component, nutrition is believed to play a vital role in the prevention and ongoing management of OA. Dietary macronutrients include lipids (fatty acids [FA]), proteins (amino acids), and carbohydrates (sugars, starchy carbohydrates, and fibrous carbohydrates). In addition to providing substrates for bioenergetic processes and raw materials for structural components of cellular biological molecules, they are known to create dynamic changes in hormones, cytokines, nutrigenomic signaling, and the neuroendocrine immune axis **[7-10]**.

In light of the above, this article aimed to analyze the available evidence on the prevention and treatment of knee OA with dietary interventions that may play a potential role in disease management. Furthermore, it sought to understand the role of free radicals in knee osteoarthritis. As the evidence base supporting the use of nutritional and metabolic optimization in musculoskeletal medicine continues to develop, clinicians will be better able to care for their patients by judiciously integrating nutritional intervention into their treatment armamentarium.

Methods

Study Design

This study followed the international systematic review model, following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) guidelines. Available at: http://www.prisma-statement.org/?AspxAutoDetectCookieSupport=1. Accessed on: March 17, 2025. The AMSTAR-2 (Assessing the Methodological Quality of Systematic Reviews) methodological quality standards were also followed. Available at: https://amstar.ca/. Accessed on: March 17, 2025.

Search Strategy and Search Sources

The literature search process was conducted from January to March 2025 and was based on Scopus, PubMed, Science Direct, Scielo, and Google Scholar, covering scientific articles from various periods to the present day. The following descriptors (DeCS/MeSH Terms) were used: *"Osteoarthritis. Knee. Nutritional approach. Prevention. Treatment"* and the Boolean "and" between MeSH terms and "or" between historical findings were used.

Study Quality and Risk of Bias

Quality was classified as high, moderate, low, or very low based on the risk of bias, clarity of comparisons, precision, and consistency of analyses. The most evident emphasis was placed on systematic review articles or meta-analyses of randomized controlled trials, followed by randomized clinical trials. Low-quality evidence was attributed to case reports, editorials, and brief communications, according to the GRADE instrument. Risk of bias was analyzed according to the Cochrane instrument by analyzing the funnel plot (sample size versus effect size), using Cohen's d test.

Results and Discussion

Summary of Findings

As a corollary to the literature search system, a total of 154 articles were found and submitted to eligibility analysis. Subsequently, 29 of the 58 final studies were selected to comprise the results of this systematic review. The selected studies were of medium to high quality (Figure 1), considering, first, the level of scientific evidence of studies in study types such as meta-analysis, consensus, randomized clinical, prospective, and observational. Biases did not compromise the scientific basis of the studies. According to the GRADE instrument, most studies presented homogeneity in their results, with X^2 = 69.7%>50%. Considering the Cochrane risk of bias tool, the overall assessment resulted in 42 studies with a high risk of bias and 24 studies that did not meet the GRADE and AMSTAR-2 criteria.

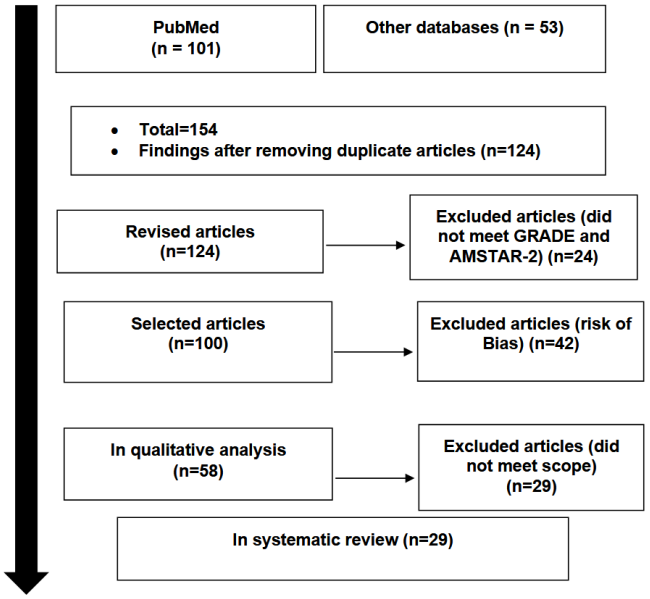

Figure 1. Flowchart showing the article selection process. Source: Own Authorship.

Figure 2 presents the results of the risk of bias of the studies using the funnel plot, showing the calculation of the effect size (magnitude of the difference) using Cohen's d test. Precision (sample size) was determined indirectly by the inverse of the standard error (1/Standard Error). This graph displayed symmetrical behavior, suggesting no significant risk of bias, either among studies with small sample sizes (lower precision), shown at the bottom of the graph, or among studies with large sample sizes, shown at the top.

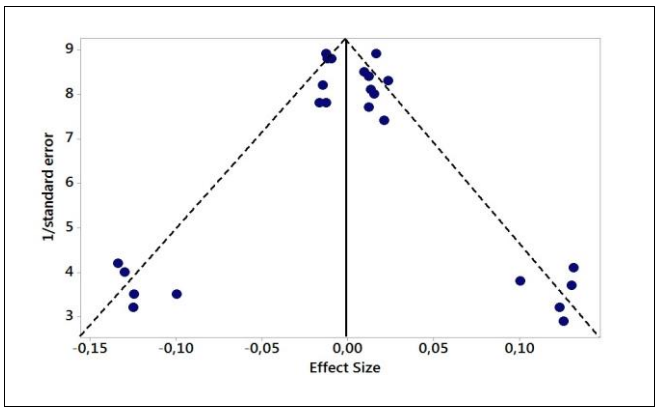

Figure 2. The symmetrical funnel plot suggests no risk of bias among the small sample size studies shown at the bottom of the graph. High-confidence and highly recommended studies are shown above the graph (n=29 studies). Source: Own authorship.

Key Considerations and Clinical Findings

The Pathophysiology of Knee Osteoarthritis

Arthritis is a disease that causes disability due to pain and inflammation in the joints. Among the different types of arthritis, rheumatoid arthritis and osteoarthritis (OA) are the most common. Osteoarthritis is an inflammatory disease that affects large joints such as the hips, knees, and hands **[1-3]**.

The causes of osteoarthritis can be diverse, including genetic predisposition, aging, obesity, trauma, and systemic diseases. Excess weight and aging increase the risk of developing knee OA **[4]**. Regardless of the etiology, several processes that occur in the early stages may involve cellular and structural changes. Osteoarthritis promotes cartilage loss, thickening of the subchondral bone, decreasing bone mass, and the formation of new osteophytes. These changes can lead to the development of bone cysts and bone marrow lesions. Subsequently, the cartilage layer may calcify, and cracks may occur. An early increase in bone remodeling and loss, followed by densification, is characteristic of the pathogenesis of OA **[5]**.

It is often stated that articular cartilage protects the bone to prevent damage during movement. However, the articular cartilage, subchondral plate, and trabecular bone are a biologically and functionally inseparable osteochondral unit that absorbs and distributes loads across the joint **[1,2]**. The osteochondral plate should be viewed as an exchange area between bone and cartilage, through which the bone supplies nutrients and oxygen to the cartilage. Due to this contact between bone and cartilage, any change in either tissue will influence the other component. The distance between the two bones is important because a decrease in this distance can increase friction during movement. Muscles and joints are vascularized and innervated, so changes in the elements in the blood supply can also influence joint properties **[5,6]**.

The abnormal mineralization that occurs may be caused by the overproduction of type I collagen by osteoblasts. This type I collagen (α1) has a lower affinity for calcium than type I collagen (α1)2 α2 **[1]**. The chemical compositions and quality of collagen differ between subchondral bone in advanced OA and in the distal femur without osteoarthritis. 18 There may also be changes in parathyroid hormone-induced cAMP levels and in vitamin D-induced production of phosphatase and osteocalcin. OA osteoblasts produce more insulin-like growth factor-1 and urokinase than normal cells. Other changes in subchondral osteoblasts in OA may include altered production of interleukin (IL)-6, IL-8, metalloproteases, and transforming growth factor (TGF-β). Increased Wnt signaling in subchondral bone may also contribute to the development of OA. There is a connection between the various tissues of the osteochondral unit, and

therefore, changes in the subchondral bone can affect the cartilage, and vice versa **[7-10]**.

Knee OA affects the entire joint: cartilage is damaged, the underlying subchondral bone structure is remodeled, and chronic inflammation develops **[3]**. OA is believed to be a chronic inflammatory disease that occurs with gradual changes in the immune system. The progression of OA involves changes in the production and function of several cytokines. The cytokines involved may be inflammatory interleukins (IL-1β, IL-6, IL-15, IL-17, and IL-18) and tumor necrosis factor alpha (TNF-α), or anti-inflammatory interleukins (IL-4, IL-10, and IL-13). Increased IL-1β causes damage to articular cartilage. The effect of TNF-α is similar and synergistic to the actions of IL-1β. The end result is a blockade of the synthesis of proteoglycan components, proteoglycan-binding proteins, and type II collagen in chondrocytes. Activated chondrocytes also produce matrix metalloproteases MMP-1, MMP-3, and MMP-13 **[4]**.

The effect of IL-6 on cartilage is similar and synergistic with that of other inflammatory cytokines, leading to a decrease in type II collagen synthesis and an increase in metalloprotease activity. Serum IL-5 concentrations have been associated with pain severity in OA **[6]**. However, synovial fluid concentrations are higher in patients with early knee OA compared with end-stage OA. IL-17 levels increase in serum and synovial fluid; this level correlates positively with radiographic findings in OA lesions. IL-18 affects chondrocytes and synovial cells, increasing the levels of several inflammatory compounds. Anti-inflammatory cytokines act primarily by decreasing the levels of inflammatory cytokines, especially IL-1 beta and TNF-a. Thus, there is sufficient evidence to support the immune hypothesis in OA **[7,8]**.

Current Therapies for Treating Osteoarthritis

There are several treatments for managing knee osteoarthritis. Non-pharmacological treatments include lifestyle changes, exercise, physical therapy, weight loss, physical aids (braces, canes, and walkers), and surgical joint replacements. Massage with and without pharmacological agents can also provide benefits **[9]**.

Physical aids can improve patients' mobility and allow for greater physical activity. Furthermore, weight loss is the primary recommendation of healthcare professionals for managing OA. A variety of exercises can be performed by patients with knee OA. Exercises involving slow, supervised movements or isometric exercises can be effective and also have a lower risk of joint damage than other exercises **[9]**. Therefore, aquatic exercise and yoga are recommended, and treadmill activities and other impact exercises should be avoided. The type, intensity, and dose of exercise can benefit each patient differently, so physical therapy is often used to determine the type and extent of exercise **[10]**.

Pharmacological agents are also used to manage OA. Temporary pain relief and, therefore, improved function can be achieved through analgesics, but this is not specific to OA. Nonsteroidal anti-inflammatory drugs are used orally and topically because they have some effects in combating inflammation and pain. However, they can have serious adverse effects with prolonged use. However, the combination of glucosamine sulfate and chondroitin sulfate is the most indicated treatment. This treatment can be effective for pain relief, functional improvement, and also result in reduced joint space narrowing **[11]**.

Oxidative stress can play an important role in several diseases, but the benefits of different antioxidant supplements may be unique to each disease. Recent literature demonstrates several benefits of antioxidants for human health, a fact that will be discussed below through the main nutritional approaches in the treatment of knee osteoarthritis **[10,11]**.

The Influence of Free Radicals on Knee Osteoarthritis

In biological systems, a free radical that involves oxygen is called a reactive oxygen species (ROS). Normal physiological processes result in the generation of ROS, such as peroxide, superoxide, hydroxyl radical, and peroxynitrite **[12]**. Thus, ROS normally occur in the body in very low concentrations (nanomolar to micromolar). They are a necessary evil, as our body needs them to survive, but when in excess, they can have deleterious effects. Our body rids itself of excess ROS using natural antioxidants such as vitamin C, vitamin E, glutathione, and various enzymes. The term oxidative stress is used as a measure of overall ROS status. It is the ratio of the amount of peroxide present to the cell's antioxidant capacity. High levels of oxidative stress can damage cells by oxidizing lipids and altering DNA and protein structure **[12]**.

Kinetic constraints indicate that in vivo ROS scavenging is ineffective as an antioxidant defense. The concept fails to consider that damage may be unique to each ROS in different cell types. Furthermore, individual ROS species can often act as signals. Therefore, a better concept of oxidative stress is that of a disruption of signaling and redox reactions. Regarding knee OA, these would be the effects on the synovium, cartilage, and joints, with effects directly related to the pathophysiology of OA **[13]**. For example, IL-1β is one of the most active cytokines during the development of OA and stimulates the

production of ROS, such as peroxides and hydroxylated radicals, and the production of nitric oxide (NO), as well as SOD deficiency. SOD deficiency leads to higher superoxide levels. NO and superoxide react to form peroxynitrite **[12]**.

Peroxynitrite can cause telomere erosion by targeting guanine repeats in DNA. The net result is a decrease in collagen II synthesis, which is necessary for cartilage maintenance. Another potential pathway by which ROS can damage the joint is through lipid peroxidation, which produces 4hydroxynonenal. Higher levels of 4-hydroxynonenal are present in OA synovial cells compared with those of healthy individuals. OA patients exhibit 4-hydroxynonenal, which inhibits collagen II expression and increases the levels of factors that can cause its degradation. Thus, 4-hydroxynonenal production by ROS could play an important role in OA. The joint is a system in which cartilage, bone, ligaments, and synovium form a capsule, and there is sufficient cross-linking between all tissues. Diffusion of ROS and lipid peroxidation products can occur between them. Thus, damage to one element of the joint can influence others through fluid diffusion and paracrine factors **[13]**. The role of ROS in the pathophysiology of knee OA provides the rationale that suppressing ROS levels with appropriate antioxidant supplements may slow disease progression **[2,3]**.

Nutritional Approach to the Treatment of Osteoarthritis

Polyunsaturated Fatty Acids

A Western-type diet, rich in red meat, high-fat dairy products, and refined grains, has been associated with higher levels of CRP and IL-6 (a pro-inflammatory diet), in contrast to the Mediterranean diet, rich in FSH and rich in whole-grain proteins, which is associated with lower levels of inflammation. The Veronese14 longitudinal cohort study with a 4-year follow-up period demonstrated that greater adherence to the Mediterranean diet is associated with a lower risk of worsening pain and symptomatic forms of knee OA **[14]**.

Lipids are stored in the matrix and chondrocytes of articular cartilage and can contribute to inflammation, cartilage degradation, and damaged chondrocyte structure. OA joints accumulate high levels of omega-6 fatty acids (n-6), precursors of pro-inflammatory eicosanoids. In individuals with established osteoarthritis or at high risk for knee OA, a positive association was observed between the n-6 polyunsaturated fatty acid (PUFA) arachidonic acid (AA) and synovitis, but an inverse relationship was observed between total plasma n-3 PUFA, docosahexaenoic acid (DHA), and patellofemoral cartilage loss, as measured by magnetic resonance imaging **[15]**.

With diet influencing systemic lipid levels, it is plausible that dietary manipulation could affect articular cartilage composition and structural damage in knee OA. A large prospective study in patients with OA found that higher intakes of total and saturated fat were associated with increased loss of knee joint width, while higher intakes of monounsaturated fatty acids (MUFAs) and PUFAs were associated with reduced radiographic progression **[16]**.

Eicosanoids are hormone-like agents that mediate and regulate inflammation. EPA and DHA create less potent inflammatory eicosanoids than those formed by n-6 series acids. Indirectly, longchain (LC) n-3 PUFAs decrease the production of pro-inflammatory eicosanoids, reactive oxygen and nitrogen species, and cytokines, while also generating anti-inflammatory mediators **[16]**.

Antioxidants and Knee Osteoarthritis

There is a plausible rationale for the role of antioxidants in OA. Reactive oxygen species and reactive nitrogen species may be involved in the pathophysiology of OA, and therefore, suppressing them with antioxidants may delay their onset and progression. The antioxidant vitamins A, C, and E are the most important, with vitamin C being particularly relevant due to its requirement for collagen formation **[17]**.

In addition to vitamins A, C, and E, vitamin D, a hormone, has many biological roles. Its main function is believed to be the regulation of bone metabolism and calcium homeostasis. Most of its activity occurs through vitamin D receptors (VDRs), a subfamily of nuclear receptors that regulate gene expression, to which it binds with high affinity **[18,19]**. Acting through VDRs, vitamin D plays an important role in the regulation of mineral homeostasis and bone metabolism. Thus, inadequate vitamin D status is believed to impair the bone's ability to respond to the pathophysiological process of OA and influence disease progression. Vitamin D may also have effects on inflammation and cytokine synthesis. Furthermore, vitamin D supplementation has positive effects on muscle strength, which may be beneficial in OA, which is often associated with marked quadriceps muscle weakness **[19]**.

Another important vitamin is vitamin K, which is part of a group of fat-soluble compounds with two natural forms, vitamin K1 (phylloquinones) and vitamin K2 (menaquinones). Vitamin K1, synthesized by plants and algae, is the most widely found form in the human

diet, primarily in green leafy vegetables and oils. Vitamin K2 is predominantly produced by bacteria [20]. In addition to its role in the complement cascade, vitamin K is involved in bone and cartilage mineralization; It is a cofactor for the enzyme γ-glutamyl carboxylase, responsible for the γcarboxylation and functionality of vitamin K-dependent (VKD) proteins. VKD proteins found in bone and cartilage include matrix Gla protein, periostin, Gla-rich protein, gas 6, and osteocalcin. Inadequate vitamin K intake can lead to decreased carboxylation of these VKD proteins, affecting their functional status and resulting in abnormalities parallel to those observed in OA [20].

Among minerals, magnesium is the second most abundant intracellular cation and one of the most important micronutrients for human health, strongly associated with immune responses. A likely link between magnesium and OA is believed. Reduced levels of magnesium and calcium were found in areas of OA in a study of women. It is postulated that magnesium deficiency may cause abnormal growth of high-calcium crystals in cartilage, causing damage to this tissue. Magnesium appears to promote the differentiation and viability of chondrocytes [21].

Furthermore, magnesium has been associated with the immune response, and reduced dietary magnesium levels have been associated with elevated levels of C-reactive protein and other inflammatory markers, suggesting a role for low-grade inflammation that could contribute to the initiation and progression of OA [22]. A cross-sectional study found an inverse relationship between magnesium intake and the radiographic incidence of knee OA in White participants, but not in Black individuals [23-25], and a prospective cohort study of patients with knee OA showed that low magnesium intake was associated with greater pain and worse functional test results [24-26]. Selenium is an essential micronutrient for various biological functions and is associated with various organic molecules, including selenocysteines, which are necessary for the function of selenoproteins involved in regulating epiphyseal plate differentiation and also in antioxidant functions [27].

The role of other nutrients in cartilage metabolism and OA is still being studied [28,29]. For example, zinc is a structural component of various proteins and, together with its transport molecules, appears to be involved in the regulation of enzymes that degrade the articular cartilage matrix, such as metalloproteinases. Excessive iron accumulation has been associated with the development of knee OA [25].

Conclusion

It was concluded that the aging population and the current obesity epidemic predict an increase in the global burden of osteoarthritis, especially knee osteoarthritis. Given the current paucity of treatment options, any approach that can reduce progression or alleviate debilitating symptoms in such a large group of patients should be evaluated. Despite the limitations of the evidence, this review may offer some guidance. Dietary modification to achieve weight reduction, along with appropriate physical activity, is an important recommendation for knee osteoarthritis. Dietary lipid modification (increasing omega-3 and reducing omega-6 intake), along with serum cholesterol reduction in osteoarthritis, is an emerging strategy with potential benefits. Furthermore, vitamins and micronutrients have a plausible role in the prevention and reduction of osteoarthritis, especially as complementary therapies.

CRediT

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The authors declare no conflict of interest.

Similarity Check

It was applied by Ithenticate®.

Application of Artificial Intelligence (AI)

Not applicable.

Peer Review Process

It was performed.

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