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Nutritional approach in the prevention and treatment of knee osteoarthritis: a systematic review

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Abstract

Osteoarthritis (OA) is the most prevalent joint disease, considered the rheumatic condition with the greatest consequences in terms of socioeconomic impacts, especially knee osteoarthritis since it makes walking difficult. To date, there is no cure for OA, so available treatments aim to reduce symptoms such as pain and inflammation, maintain joint mobility, and limit the loss of function. As OA has a known inflammatory component, it is believed that nutrition can play a vital role in the prevention and ongoing management of OA. This article aims to analyze the available evidence in the prevention and treatment of knee OA with a dietary intervention that may play a potential role in the management of the disease. To carry out this literature review, articles were searched in the Scielo, Pubmed, and Bireme databases with the time frame of the last 10 years. The results showed that some nutrients, vitamins, and antioxidants are widely discussed in the literature in the treatment and prevention of the disease. Management of free radicals is necessary and the influence of nutrients and diet on cartilage and OA metabolism may represent a long-term adjuvant alternative in the treatment of patients with knee OA. 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, considered the rheumatic condition with the greatest consequences in terms of socioeconomic impacts, especially knee osteoarthritis since it makes walking difficult. The incidence of the disease increases with age, evolving over decades until the loss of joint function is reached. In addition, elderly patients have several comorbid conditions that increase the complexity of treatment [1,2].

To date, there is no cure for OA, so available treatments aim to reduce symptoms such as pain and inflammation, maintain joint mobility, and limit the loss of function. Several international guidelines have been published with recommendations for the management of knee osteoarthritis, in all guidelines, the recommendation presents non-pharmacological and pharmacological approaches. Non-pharmacological interventions include weight reduction, adequate physical activity, physical therapy, muscle strengthening, mobility aids, knee pads, shoes and insoles, electrical stimulation, and acupuncture, in addition to pharmacological treatments [3].

There is a great need for OA prevention. The first step is to pursue a healthy lifestyle, weight loss, and nutrition with specific nutrients that can help achieve this goal. In addition, several foods can help prevent or treat OA, using them as an adjunct to treatment. There are several emerging alternatives, it is increasingly recognized that nutritional strategies can help maintain healthy bones and joints [3].

The pathophysiology of OA is now recognized to involve much more than the simple mechanical wear of the articular cartilage. It involves a complex interaction between pro-anti-inflammatory joint mediators, as well as anabolic versus catabolic signaling in chondrocytes,

cartilage matrix, synovia, and synovial fluid. Pro-inflammatory cytokines, in addition to local and systemic factors such as oxidative stress due to decreased antioxidant capacity of joints, play important roles in the pathobiology of OA and cartilage metabolism [4].

As OA has a known inflammatory component, it is believed that nutrition can 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 substrate for bioenergetic processes and raw material for structural components of cellular biological molecules, they are known to create dynamic changes in hormones, cytokines, nutrigenomic signaling, and in the neuroendocrine-immune axis [1].

Therefore, this article analyzed the available evidence in the prevention and treatment of knee OA with a dietary intervention that could play a potential role in the management of the disease. Also, it will seek 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 arsenal.

Methods

Study Design

The rules of the Systematic Review-PRISMA Platform (Transparent reporting of systematic reviews and meta-analysis-HTTP: //www.prisma-statement.org/) were followed [5].

Data sources and research strategy

To carry out this literature review, articles were searched in the Scielo, Pubmed, and Bireme databases. The keywords used were: knee osteoarthritis, nutritional approach, prevention, treatment, and their respective terms in English. The selected articles used as inclusion criteria the timeline of the last 10 years, covering the period from 2009 to 2021, which dealt with osteoarthritis, knee osteoarthritis, and the nutritional action in the prevention and treatment of osteoarthritis. For this, prospective, retrospective, case-control, cross-sectional, case reports, in vitro and in vivo studies were selected, in addition to systematic and literature reviews. As exclusion criteria, articles that did not relate the nutritional approach to osteoarthritis, as well as those published more than 10 years ago, were not selected.

Study Quality and Bias Risk

The quality of the studies was based on the GRADE instrument [6] and the risk of bias was analyzed according to the Cochrane instrument [7].

Results and Discussion

A total of 92 studies were found that were submitted to the eligibility analysis, and after that, 33 studies of high to medium quality and risks of bias were selected that do not compromise the scientific basis of the studies (**Figure 1**).

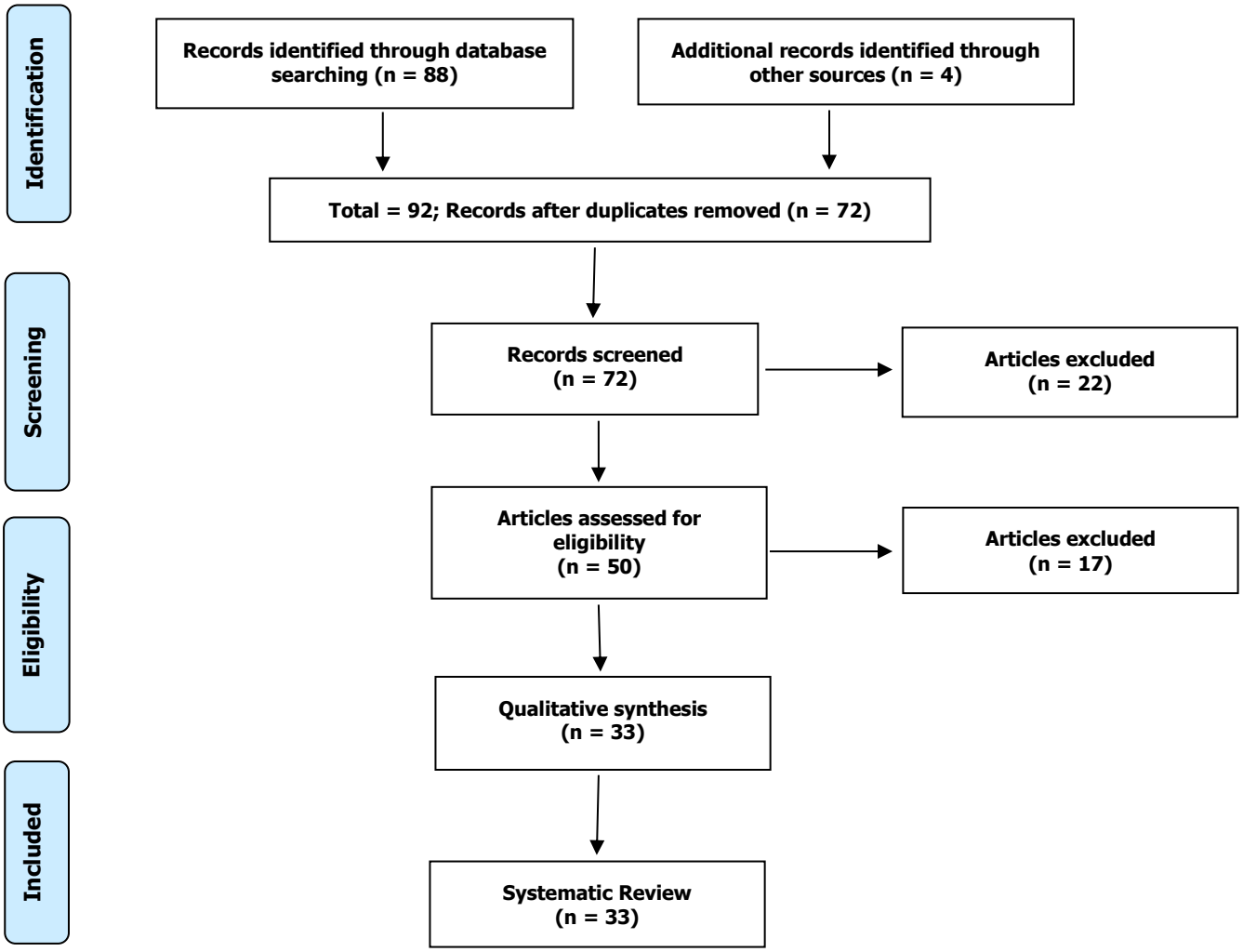
The Pathophysiology of Knee Osteoarthritis

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 types, with osteoarthritis being an inflammatory disease that affects large joints such as hips, knees, and hands [8].

The causes for the development of osteoarthritis can be diverse, such as genetic predisposition, aging, obesity, trauma, and systemic diseases. Overweight and aging increase the risk of developing knee OA [8]. Regardless of etiology, several processes that occur in the early stages can involve cellular and structural changes. Osteoarthritis promotes cartilage loss, the subchondral bone thickens, bone mass decreases, and new osteophytes are formed. These changes can lead to the development of bone cysts and bone marrow injuries. Subsequently, the cartilage layer may be calcified, and cracking may occur. An early increase in bone remodeling and loss, followed by densification are characteristic of the pathogenesis of OA [9].

It is often said that articular cartilage protects the bone to prevent damage during movement. However, articular cartilage, subchondral plate and trabecular bone are a biologically and functionally inseparable osteochondral unit that absorbs and distributes loads across the joint [1]. Osteochondral plaque should be seen as an area of exchange between bone and cartilage through which bone supplies nutrients and oxygen to the cartilage. Due to this contact between bone and cartilage, any change in any 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 elements in the blood supplied can also influence the properties of the joint [9].

Figure 1. Study eligibility.



The abnormal mineralization that occurs can be caused by the overproduction of type I collagen by osteoblasts. This collagen (α1) 3 type I has a lower affinity for calcium than collagen (α1) 2 α2 type I [1]. The chemical compositions and quality of collagen are different between the subchondral bone in advanced OA and the distal femur that does not have osteoarthritis. There may also be changes in parathyroid hormone-induced cAMP levels and vitamin D-induced production of phosphatase and osteocalcin [1]. OA osteoblasts produce more insulin-like growth factor-1 and urokinase than normal cells. Other alterations in subchondral osteoblasts in OA may be the altered production of interleukin (IL)-6, IL-8, metalloproteases, and transforming growth factor (TGF-β). Increased Wnt signaling pathway in the subchondral bone may also contribute to the development of OA [1]. There is a link between the various tissues of the osteochondral unit and, therefore, changes in the subchondral bone can affect the cartilage and the reverse can also occur.

Knee OA affects the entire joint: cartilage is damaged, the underlying subchondral bone structure is remodeled, and chronic inflammation develops [4]. It is believed that OA is 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 can be inflammatory interleukins (IL-1 β, 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). The increase in IL-1 causes damage to the articular cartilage [8]. The effect of TNF-α is similar and synergistic to the actions of IL-1 β. The result is a blockage in the synthesis of proteoglycan components, proteins that bind to proteoglycans, and type II collagen in chondrocytes. Activated chondrocytes also produce matrix metalloproteases MMP-1, MMP-3, MMP-13 [8].

The effect of IL-6 on cartilage is similar and synergistic with other inflammatory cytokines and leads to a decrease in collagen type II synthesis and an increase in metalloprotease activity [8]. Serum IL-5 concentrations have been associated with OA pain

severity [10]. However, concentrations in synovial fluid are higher in patients with early OA of the knee compared to late-stage OA [11]. The level of IL-17 increases in serum and synovial fluid, this level is positively correlated with the radiographic image of OA lesions [12]. IL-18 affects chondrocytes and synovial cells, increasing the levels of several inflammatory compounds. Anti-inflammatory cytokines act mainly 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 [8].

Therapies for the Treatment of Osteoarthritis

There are several treatments to control knee osteoarthritis. Non-pharmacological treatments include changes in habits, exercise, physiotherapy, weight loss, physical aids (braces, braces, and walkers), and surgical joint replacements. Massage with and without pharmacological agents can also provide benefits [13].

Physical aids can improve patient mobility and allow more physical activity to be performed. In addition, weight loss is the main recommendation of health professionals for the management of OA. A variety of exercises can be performed by patients with knee OA. Exercises that involve supervised slow movements or isometric exercises can be effective and also have a lower chance of joint damage than other exercises [13]. Therefore, aquatic exercises and yoga are indicated, and treadmill activities and other impact exercises should be avoided. The type, intensity, and dose of exercise can benefit each patient in different ways, so physiotherapy is often used to determine the type and extent of exercises [14].

Pharmacological agents are also used for the management of 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 fighting inflation and pain. However, they can have serious adverse effects with prolonged use. However, the combination of glucosamine sulfate and chondroitin sulfate is the most suitable for treatment. This treatment can be effective for pain relief, functional improvement and also result in less joint space narrowing [15].

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

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. Thus, ROS normally occur in the body at very low concentrations (nanomolar to micromolar). They are a necessary evil, as our bodies need them to survive, but when in excess they can have deleterious effects. Our bodies get rid 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 between the amount of peroxide present and the cell's antioxidant capacity. High levels of oxidative stress can damage cells by oxidizing lipids and altering the structure of DNA and protein [16].

Kinetic restrictions indicate that the in vivo elimination of ROS is ineffective as an antioxidant defense [16]. The concept does not consider that the damage can be unique to each ROS in different cell types. Furthermore, individual species of ROS can often act as signals. Therefore, a better concept of oxidative stress is that of an interruption of redox signaling and reaction. Treating knee OA, these would be the effects on the synovia, cartilage, and joints, with effects directly related to the pathophysiology of OA [17]. For example, IL-1 β 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) and a deficiency of SOD. SOD deficiency leads to higher superoxide levels. NO and superoxide react to form peroxynitrite [16].

Peroxynitrite can cause telomere erosion by targeting guanine repeats in DNA. The net result is a decrease in collagen II synthesis, necessary for cartilage maintenance. Another potential pathway by which ROS can damage the joint is through lipid peroxidation, which produces 4-hydroxynonenal. Higher levels of 4-hydroxynonenal are present in OA synovial cells compared to healthy individuals. OA patients exhibit, 4-hydroxynonemal inhibited collagen II expression and increased levels of factors that can cause its degradation. Thus, the production of 4-hydroxynonenal 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 are sufficient cross-links between all tissues. A 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 [17].

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.

Nutrological Approach to the Treatment of Osteoarthritis

Polyunsaturated Fatty Acids

The Western-style diet, rich in red meat, high-fat dairy, and refined grains, has been associated with higher levels of CRP and IL-6 (pro-inflammatory diet), in contrast to the Mediterranean diet, which is rich in FSH and rich in integral proteins that are associated with lower levels of inflammation. Veronese's 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 **[18]**.

Lipids are stored in the matrix and chondrocytes of articular cartilage and may contribute to inflammation, cartilage degradation, and damaged chondrocyte structure. OA joints accumulate high levels of omega-6 (n-6) fatty acids, precursors of pro-inflammatory eicosanoids. In individuals with established osteoarthritis or at high risk of knee OA, a positive association was observed between arachidonic acid (AA) from n-6 polyunsaturated fatty acid (PUFA) and synovitis, but an inverse relationship between n-6 PUFA -3 of total plasma, docosahexaenoic acid (DHA) and patellofemoral cartilage loss, measured by magnetic resonance [19].

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 OA patients 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 **[20]**. Eicosanoids are hormone-like agents that mediate and regulate inflammation. EPA and DHA create less potent inflammatory eicosanoids than those formed by the n-6 series acids. Indirectly, long-chain (LC) n-3 PUFAs decrease the production of pro-inflammatory eicosanoids, reactive oxygen and nitrogen species, and cytokines, additionally generating anti-inflammatory mediators [20]. **[20]**.

To identify the prevalence of sarcopenic obesity, a low muscle mass, and high adiposity phenotype, in adults with end-stage knee OA. Various diagnostic criteria, including assessment of muscle/fat mass, muscle strength, and physical function, were used to identify patients with and without sarcopenic obesity and to compare pain, function, and quality of life outcomes **[20]**.

Major Current Clinical Studies

A cross-sectional clinical study included adults with BMI ≥30 kg/m2 and knee osteoarthritis. 151 adults were included (59% women) aged 65.1 ± 7.9 years, mean BMI of 37.1 ± 5.5 kg/m2. Given the impact of this condition and knee osteoarthritis on physical function, it has been suggested that a combined diagnostic approach be used to clarify the expected prevalence and allow for early clinical identification and management of sarcopenic obesity in patients with this condition **[21]**.

Furthermore, curcumin is an effective ingredient in turmeric with anti-inflammatory properties and plays an important role in protecting the joints from destructive factors. Added to this, gingerols and piperine are the effective ingredients of ginger and black pepper, which can enhance and maintain the effect of curcumin for this purpose. Thus, a randomized study analyzed the effect of co-supplementation with turmeric, black pepper, and ginger extract on prostaglandin E2 (PGE2) in patients with chronic knee osteoarthritis compared to Naproxen. Sixty patients with two different levels of knee osteoarthritis (Grade 2 and 3) were studied for 4 weeks. PGE2 significantly decreased in both groups ($p<0.001$). The results of this study indicated that ingestion of selected herbs twice a day for 4 weeks can improve PGE2 levels in patients with chronic knee osteoarthritis similar to the drug Naproxen **[22]**.

Also, a systematic review and meta-analysis study evaluated the effect of nutraceutical supplementation on pain intensity and physical function in patients with knee/hip osteoarthritis. A total of 42 randomized controlled trials were involved in the meta-analysis. Through these analyses, it was found that nutraceutical nutritional supplementation of patients with knee/hip osteoarthritis can lead to an improvement in pain intensity and physical function **[23]**.

Besides, aging and osteoarthritis are associated with a high risk of muscle wasting and physical disability. In this sense, a meta-analysis study observed the effectiveness of protein supplementation combined with exercise training (PS + TE) in improving muscle mass and functional outcomes in elderly people with lower limb osteoarthritis. Six randomized controlled trials were included. The PS + ET group exhibited significant improvements in muscle mass, pain, and muscle strength. Thus, PS + ET improves muscle mass, muscle

strength, and functional outcomes and reduces pain in older adults with lower limb osteoarthritis [24].

Antioxidants And Knee Osteoarthritis

There is a plausible rationale for explaining 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 its onset and progression. Antioxidant vitamins A, C, and E are the most important, with vitamin C being particularly relevant due to its need for collagen formation [25]. In addition to vitamins A, C, and E, vitamin D, which is a hormone, has many biological roles, its main function is believed to be the regulation of bone metabolism and calcium homeostasis [26]. 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 [27].

Acting through VDRs, vitamin D plays an important role in regulating mineral homeostasis and bone metabolism. Thus, it is believed that inadequate vitamin D status impairs 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 and this may be beneficial in OA, which is often associated with marked weakness of the quadriceps muscles [27].

Another important vitamin is vitamin K, which is part of a group of fat-soluble compounds, with two natural forms, vitamin K1 (phylloquinone) and vitamin K2 (menaquinones). Vitamin K1, synthesized by plants and algae, is the form most widely found in the human diet, mainly in green leafy vegetables and oils. Vitamin K2 is predominantly produced by bacteria [28]. In addition to its role in the complement cascade, vitamin K is involved in bone and cartilage mineralization; is a cofactor for the γ-glutamyl carboxylase enzyme, responsible for the γ-carboxylation and functionality of vitamin K-dependent proteins (VKD). 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 the functional status and resulting in abnormalities parallel to those observed in OA [28].

Among minerals, magnesium is the second most abundant intracellular cation and one of the most important micronutrients for human health and is strongly associated with immune responses. It is believed that there is a probable relationship between magnesium and OA. Reduced levels of magnesium and calcium in OA areas were found in a study of women. It is postulated that magnesium deficiency can cause an abnormal growth of crystals with high calcium content in cartilage causing damage to this tissue. Magnesium appears to promote chondrocyte differentiation and viability [29]. In addition, 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 in low-grade inflammation that could participate in the initiation and progression of OA [30].

A cross-sectional study found an inverse relationship between magnesium intake and radiographic incidence of knee OA in white participants but not in black subjects [31], and a prospective cohort study in patients with knee OA showed that low intake magnesium was associated with greater pain and worse functional test results [32]. Selenium is an essential micronutrient for different biological functions and is associated with different organic molecules, including selenocysteines, which are necessary for the function of selenoproteins involved in regulating epiphyseal plaque differentiation and also in the performance of antioxidant functions. The role of other nutrients in cartilage and OA metabolism is still being studied. For example, zinc is a structural component of different proteins and, together with its transport molecules, seems to intervene 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 [33].

Conclusion

Population aging and the current obesity epidemic predict an increase in the global burden of OA, especially on the knees. Given the current scarcity of treatment options, any means that can reduce progression or alleviate debilitating symptoms in such a large group of patients must be evaluated. Despite the limitations of the evidence, most of which with knee OA, this review can provide some guidance. Diet modification to achieve weight reduction, together with appropriate physical activity, are important recommended factors in knee osteoarthritis. Dietary lipid modification (increasing omega-3 intake and reducing omega-6 intake, along with lowering serum cholesterol in OA is an emerging strategy that has benefits. In addition, vitamins and micronutrients play a plausible role. in the prevention and reduction of OA, especially as complementary

therapies.

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Data sharing statement

No additional data are available.

Conflict of interest

The authors declare no conflict of interest.

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