Nutritional Interventions to Prevent and Treat Osteoarthritis. Part I: Focus on Fatty Acids and Macronutrients

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Abstract: Osteoarthritis (OA) is the most common cause of musculoskeletal disability in elderly individuals, and it places an enormous economic burden on society. Management of OA is primarily focused on palliative relief by using agents such as nonsteroidal anti-inflammatory drugs and analgesics. However, such an approach is limited by a narrow therapeutic focus that fails to address the progressive and multimodal nature of OA. Given the favorable safety profile of most nutritional interventions, identifying disease-modifying nutritional agents capable of improving symptoms and also preventing, slowing, or even reversing the degenerative process in OA should remain an important paradigm in translational and clinical research. Applying advances in nutritional science to musculoskeletal medicine remains challenging, given the fluid and dynamic nature of the field, along with a rapidly developing regulatory climate over manufacturing and commerce requirements. The aim of this article is to review the available literature on effectiveness and potential mechanism of macronutrients for OA, with a focus on the following: long-chain \( \omega-3 \) essential fatty acids eicosapentaenoic acid and docosahexaenoic acid, functional \( \omega-6 \) fatty acid \( \gamma \)-linolenic acid, and macronutrient composition of background diet. There also is a discussion about the concept of rational polysupplementation via the strategic integration of multiple nutraceuticals with potential complementary mechanisms for improving outcomes in OA. As applied nutritional science evolves, it will be important to stay on the forefront of proteomics, metabolomics, epigenetics, and nutrigenomics, because they hold enormous potential for developing novel therapeutic and prognostic breakthroughs in many areas of medicine, including OA.

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INTRODUCTION

The rising incidence of osteoarthritis (OA) places an enormous economic burden on society, with direct and indirect costs related to medical management, rehabilitation, arthroplasty, and lost occupational productivity as a result of functional disability [1]. Nutritional interventions and nutraceutical applications for medical conditions, including OA, are currently riding the crest of public enthusiasm. The medical community must be familiar with the current state of the science to evaluate the potential benefits of nutritional methods for preventing and treating OA. The integration of complementary and/or nutraceutical methods expands treatment options for patients with established OA beyond the traditional rehabilitation, bracing, medication, interventional, and surgical strategies [2]. The progression of OA is multifocal, with biomechanical, metabolic, epigenetic, and genetic risk factors; therefore, the most-effective outcomes may stem from integrating a comprehensive, multimodal treatment program early in the disease process [3]. The increasing incidence and high prevalence of OA creates an opportunity to develop and use relatively low-cost nutraceutical alternatives, with the potential for additional health benefits for other conditions and organ systems. Evidence from higher-quality scientific studies is beginning to emerge that documents both the usefulness and limitations associated with various nutritional strategies for OA [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...
articular pro- versus anti-inflammatory mediators as well as anabolic versus catabolic signaling within chondrocytes, the cartilaginous matrix, synovium, and synovial fluid [3,5]. Results from in vitro and animal investigations of OA confirmed that proinflammatory cytokines, in addition to local and systemic factors, such as oxidative stress due to decreased articular antioxidant capacity, play important roles in the pathobiology of OA and cartilage metabolism [6-10]. Nutritional strategies have made a substantial mark in the existing complementary medicine literature for managing rheumatoid arthritis (RA) [11], a condition of chronic inflammation of the synovial joints. Because OA has a known inflammatory component, it follows that nutrition may play a vital role in the prevention and ongoing management of OA. RA has also been treated through the development of disease-modifying drugs that target the proinflammatory cytokines interleukin (IL)-1 and tumor necrosis factor–α (TNF-α). The development of disease-modifying OA drugs may logically follow the RA paradigm by targeting IL-1 and TNF-α [12,13].

The dietary macronutrients include lipids (fatty acids [FA]), protein (amino acids), and carbohydrates (sugars, starchy and fibrous carbohydrates). Beyond providing substrate for bioenergetic processes and raw material for structural components of cellular biologic molecules, they are known to create dynamic changes in hormones, cytokines, nutrigenomic signaling, and the neuro–endocrine–immune axis [4,11,14]. This review focuses on FAs as the major macronutrient with the potential to support and influence the structure and function of joints. In addition, the consumption of specific types of FAs with certain ratios of polyunsaturated FAs has been linked to immunomodulation and key biochemical processes associated with OA [15,16].

This article reviews the best available evidence for treating OA with strategic dietary and nutraceutical intervention, in addition to discussing other nutrients that may have a potential role in prevention. As the evidence base that supports the use of nutritional and metabolic optimization in musculoskeletal medicine continues to develop, physicians will be better able to serve their patients by judiciously integrating nutritional intervention into their treatment armamentarium.

**REVIEW OF LIPID BIOCHEMISTRY**

FAs are a type of lipid that are derived from triglycerides or phospholipids. They are classified based on the number of double bonds between the carbon atoms. Without any carbon double bonds, the FA is considered “saturated” with hydrogen atoms. With one double bond, the FA is monounsaturated (MUFA), and, with multiple double bonds, the FA is polyunsaturated (PUFA). FAs also vary in their carbon tail length: short-chain FAs (<6 carbons long), medium-chain FAs (6-12 carbons long), long-chain (LC) FAs (13 carbons long), to very-LC FAs (>13 carbons long). Highly unsaturated FAs (HUFA) are PUFS with carbon chain lengths longer than 20, and 4 or more double bonds. PUFAs are further classified as long-chain ω-3 (n-3) or functional ω-6 (n-6), depending on the position of the last double bond, counting from the distant methyl end along the FA chain. In n-3, this last double bond is located between the third and fourth carbon atom from the methyl end of the FA chain. The main dietary PUFAs are n-3 (such as α-linolenic acid [ALA]) and eicosapentaenoic acid (EPA), and n-6 (such as linoleic acid [LA] and arachidonic acid [AA]). The ω-3 (an n-3 PUFA) is found in canola oils, flaxseeds, walnuts, and fish oils, whereas n-6 is found in safflower, corn, soybean, and sunflower oils as well as in meat. Oleic acid, an ω-9 (n-9) FA, is the most abundant MUFA in the human diet. MUFA-rich food sources include: olive oil, olives, most nuts, canola oil, and avocados among others. Scientific abbreviations for FAs tell something about their chemical structure, such as length of the aliphatic carbon tail, the number of double bonds, and location of double bonds. One scientific abbreviation for ALA is 18:3n-3. The first part (18:3) indicates an 18-carbon FA with 3 double bonds, whereas the second part (n-3) indicates that the first double bond is in the n-3 position, which defines it as an ω-3 FA.

Humans and other mammals can synthesize saturated FAs and some MUFS from carbon groups in carbohydrates and proteins, but they lack the enzymes necessary to insert a cis double bond at the n-6 or the n-3 position of an FA. Consequently, n-6 and n-3 FAs are essential nutrients. Two essential FAs that cannot be produced by the human body are the n-6 LA and the n-3 ALA. The human body has a limited ability to convert ALA into the longer-chain n-3 FAs EPA and DHA. PUFAs are used as substrates for synthesis of biologically active compounds, such as steroid hormones, prostaglandins (PG), and leukotrienes (LT). Saturated fat is preferentially incorporated into adipose tissue stores because the absence of double bonds yields a higher energy density than is obtained from oxidation of unsaturated FAs. MUFS are either oxidized for energy or stored as fat, depending upon the demand for energy.

EPA or DHA are the LC n-3s found predominantly in marine food sources or purified fish oil supplements. When these FA precursors are used as substrates for the cyclooxygenase (COX) and lipoxigenase (LOX) enzyme pathways, the metabolic end products (eicosanoids and docosanoids) have anti-inflammatory properties due to their different structures and functions (Figure 1). However, when the initial substrate for the COX and LOX pathways are derived from the n-6 FAs LA and AA, the downstream end products possess proinflammatory characteristics. Although a sufficient intake of n-6 FAs plays an important role in cellular membrane structure and function, and n-6 FAs act as precursors for bioactive hormones and eicosanoids, excessive levels of n-6 FAs relative to the n-3s are known to shift the eicosanoid profile toward one that is proinflammatory, prothrombotic, and proinvascrotective (Figure 1).
POTENTIAL MECHANISMS OF ACTION

Most diets in the developed world provide suboptimal amounts of n-3 PUFA, with the standard American diet providing an \( \omega-6 \) (n-6) to n-3 PUFA ratio as high as 20:1, as opposed to the 4:1 to 1:1 ratio that has been proposed for optimal health [17-20]. One of the established mechanisms by which fish oil has been shown to decrease inflammation is by modifying the class of autacoids that are produced via FA metabolism through COX- and LOX-mediated biochemical pathways, from 2-series to 3-series PGs and 4-series to the 5-series LTs (Figure 2). There are emerging novel mechanisms by which the n-3 FAs, EPA and DHA, are delivering a biologic effect, which is in addition to their known effects of both inhibiting the proinflammatory AA (n-6 PUFA) derived PGs (PGE2) and leukotrienes (LTB4), and stimulating the synthesis of anti-inflammatory autacoids (PGE3 and LTB5). These emerging mechanisms involve a flux of the n-3 FAs EPA and DHA through biochemical pathways that create bioactive lipid epoxide products known to have potent anti-inflammatory activity via their interaction with G-protein–coupled receptors [21-23].

Specialized downstream lipid mediators of eicosanoid metabolism are now touted as being critical to transitioning through a controlled inflammatory response and ultimately a resolution of the inflammatory cascade to achieve a state of tissue homeostasis [24]. These unique lipid mediators are

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**Figure 1.** Sources and metabolic destinations of \( \omega-3 \) and \( \omega-6 \) polyunsaturated fatty acids.

**Figure 2.** Fish oil’s potential triad of mechanisms for mitigating osteoarthritis.
simply the oxygenated biochemical FA end products further downstream of PGs and LTs derived from metabolic pathways by using EPA and DHA as the substrates. The 4 main families of these endogenous, specialized lipid mediators are known as lipoxins, resolvins, protectins, and maresins. The novel anti-inflammatory and proresolving mediators help with signaling the termination of acute inflammation in the injured cells and tissues. They may counter a chronic, non-functional inflammatory state through their interaction with serpentine transmembrane G-protein receptors on various cell types [23]. Hence, suboptimal consumption of the n-3 PUFA or overconsumption of n-6 PUFA leads to an imbalance in the eicosanoid “milieu,” which favors a chronic inflammatory state that promotes joint dysfunction and degeneration [25]. However, both EPA and DHA are competitor substrates that inhibit oxidation and metabolism of n-6 AA by the COX and LOX enzymes.

The essential FAs in fish oil also provide the plasma membrane with structural support for repairing and remodeling tissue that has been damaged or degenerated. Essential FAs provide necessary chemical building blocks for restoring structural integrity and function to articular cartilage chondrocytes, in addition to maintaining synoviocyte function [26,27] (Figure 2).

Although it is still speculative, n-3 LC PUFA–rich fish oil may round out a “therapeutic triad” for OA pain by influencing the peripheral and central nervous systems (Figure 2). The ω-3–rich FAs may play a role in stabilizing aberrant neuronal membrane thresholds and in addressing nociceptive afferent signaling. There is preliminary scientific evidence that promotes joint dysfunction and degeneration as a result of sufficient LC n-3 FAs [28]. Because pain transmission is dependent on neuroactive metabolites of n-6 AA, ion channel currents, and membrane function, there may be an emerging role for their competitive inhibitors. The n-3 FAs EPA and DHA in fish oil may effectively modulate the abundance and metabolism of n-6 AA in nerve, immune, and synovial tissues. They, therefore, may have potential benefits in chronic OA and also other complex, persistent pain syndromes [29]. Furthermore, increasing n-3 EPA and DHA intake and/or decreasing n-6 LA or AA consumption may increase the abundance of neuroprotectin and resolvin downstream lipid metabolites that are known to possess analgesic properties [30]. A secondary aspect of long-standing OA is the prevalence of depression, fear, and anxiety, which may exacerbate the severity of functional impairment and disability [31,32]. Fish oil supplementation has been shown to provide targeted nutritional support for reducing symptoms of depression and anxiety in various patient populations [33-35].

Finally, obesity is heavily associated with OA incidence and severity in a manner that is out of proportion with mechanical overload and abnormal joint stresses [36]. As such, there is accumulating evidence that the adipokine profile present in individuals with metabolic syndrome and obesity, which includes leptin, resistin, visfatin, TNF-α, IL-6, and adiponectin, is contributing to the pathobiology of OA [37]. Fish oil consumption rich in n-3 LC PUFA has been shown to modulate and improve the adipokine population toward one that is less proinflammatory and more supportive of chondrocyte and synovial health [13].

**ESTABLISHED EVIDENCE BASE FOR FISH OIL IN RA**

There is a growing body of animal, in vitro, and clinical evidence that shows that the ω-3 (n-3) LC PUFA, particularly from fish, may significantly modulate inflammatory signals, thereby decreasing joint pain and improving joint function [25]. With respect to the use of fish oil for joint health, the majority of the clinical evidence has been endorsed in RA, with more than 15 human randomized, controlled clinical trials and multiple meta-analyses that show improvements in pain and/or joint function [38-44]. Anti-inflammatory benefits of n-3 HUFAs have been demonstrated, with decreases in proinflammatory PG, LT, thromboxanes, and cytokines TNF-α and IL-1β in monocytes [45,46]. This effect of fish oil supplementation on cytokines is especially important, because TNF-α and IL-1β upregulate the release of collagenase, stromelysin, matrix metalloproteinases, and other mediators. These cytokines have been implicated in the joint damage that is the hallmark of RA and associated, to a lesser extent, with OA [45,47,48]. Fish oil supplementation in RA has also been associated with reduced morning stiffness, decreased tender joint count, improved functional status, and reduced nonsteroidal anti-inflammatory drug use [49,50].

**EMERGING EVIDENCE FOR USE OF n-3 FAs IN OA**

Given our current understanding of the pathobiology of OA and the emerging science that supports the molecular overlap between RA and OA, the potential influence of dietary n-3 LC HUFA on the occurrence and progression of OA is obvious and must be explored further. Although in vivo data are lacking, the inhibitory effects of n-3 LC HUFA on chondrocyte-derived enzymes implicated in the pathogenesis of OA [51] provide ample rationale for further investigation in humans with OA or at risk for developing OA. Also, when considering the emerging basis for broad recommendations to increase dietary n-3 PUFA intakes for cardiovascular benefit, the possible positive effects of fish oil and/or n-3 LC HUFA on OA need to be defined. In addition to the credence of using LC n-3 HUFA in OA, Knott et al [52] have recently published data derived from a spontaneous OA guinea pig model to characterize the effects of an n-3-FA–rich diet on biomarkers of OA within both articular cartilage and subchondral bone. The n-3–rich diet was found to improve...
histologic and biochemical markers of OA, including matrix metalloproteinase (MMP)-2, collagen cross-links, denatured type II collagen, glycosaminoglycan content, and subchondral bone density.

SUPPLEMENTATION AND DIETARY CONSIDERATIONS

Satisfying ω-3 daily recommendations through diet alone are difficult due to the increasing presence of heavy metals, polychlorinated biphenyls, dioxins, and other environmental toxins in the fresh fish supply. Hence, supplementing with n-3 fish oil that is third-party tested for purity, potency, and freshness may provide a safe and effective method of addressing a relative n-6 to n-3 imbalance or relative ω-3 PUFA insufficiency [53,54]. Furthermore, increasing the consumption of the n-3 fish oil rich in EPA and DHA positively contributes to a wide range of other benefits beyond joint health, including cardiovascular health, cognitive function, mood, immune function, inflammatory bowel disease, metabolic health, muscular strength and function, vision, and osteoporosis [55-60]. Although administration of fish oil supplements provides an effective way to increase tissue levels of n-3 LC HUFA by modifying whole food nutrition in the background diet by selecting foods rich in n-3 PUFA, and avoidance of unnecessary amounts of n-6 PUFA can improve and enhance n-3 FA tissue status and cell membrane incorporation. Cleland et al [61] established that tissue EPA and DHA levels can be increased through changes in background diets in a series of investigations in which healthy volunteers consumed fats rich in n-3 while restricting those rich in n-6 (vegetable spreads, cooking oils, and dressings). Furthermore, this background diet enhanced incorporation of n-3 LC HUFA from fish oil supplements due to the competitive nature of these rival substrates for multiple enzymatic pathways [61-63]. These data underscore the importance of overall diet, despite the strong evidence of efficacy that supports fish oil supplementation.

Kril oil supplements have gained notoriety among the general population and the scientific community as an additional source of n-3 FAs. Krill are small shrimp-like crustaceans that flourish in the cold waters of the Antarctic Ocean. Unlike n-3 LC PUFA from other animal sources, a high proportion of krill oil fats are found in a phospholipid molecular form as opposed to a triacylglycerol (TAG) or ethyl esterified version, which may help explain their unique bioavailability, and potential joint health support [64,65]. In addition, krill are also a natural source of astaxanthin, a potent antioxidant carotenoid pigment providing a dark pink-red color, is being shown to have positive effects on inflammation, the cardiovascular system, and even athletic performance [66-69]. Although there are far fewer published human studies conducted with krill oil compared with fish oil, which has well over 1000 peer-reviewed human trials, data on krill are beginning to emerge. Animal data on an experimental model of inflammatory arthritis by Ierna et al [70] demonstrated that mice fed equal amounts of fish oil and krill oil in an ad libitum diet had reduced clinical arthritis scores, paw edema, and synovial proliferation on histopathology relative to the control diet group. Interestingly, only the krill group demonstrated reduced leukocyte joint and synovial infiltration, and an improved arthritis severity score in the late phase of the study. Moreover, only the fish oil group showed modulation of inflammatory cytokines in serum, whereas krill oil did not show an effect in serum [70]. A randomized double-blind clinical trial in human subjects with confirmed RA or OA of the hip and/or knee when using 300 mg of krill oil resulted in significant reductions of C-reactive protein (CRP) and pain, stiffness, and functional impairment scores of the Western Ontario and McMaster Universities Osteoarthritis Index subscales with short-term treatment effects seen at 7 days and sustained through the 30-day study period [71]. Taken together, the limited available data suggest that consuming fish oil in a larger dose to address systemic inflammation and cardioprotection, along with at least 300 mg of a complementary krill oil to target intrinsic joint inflammation and leukocytic infiltration, would be an optimal nutraceutical strategy.

The ω-3 FAs fall into 2 major categories: plant derived (eg, flax seed oil, 18:3 n-3 ALA) or marine derived (eg, fish oil, which contains both 20:5 n-3 EPA and 22:6 n-3 DHA). The human conversion of ALA to EPA and DHA is metabolically inefficient because results of research showed that less than 15% of ALA converts to EPA and less than 5% converts to DHA even under optimal conditions [72,73]. This metabolic inefficiency stems from the various factors that create suboptimal conditions for the biochemical pathways of elongating and desaturating ALA when it is the substrate. Patients who over consume n-6 FAs, trans-FAs, or alcohol, or who are on certain medications (eg, corticosteroids) are known to have a decreased ability to convert the shorter chain n-3 ALA to the longer chain EPA and DHA [73]. Additionally, those who have metabolic syndrome, insulin resistance, vitamin or mineral deficiencies (eg, B₃, B₆, C, zinc, magnesium) also have decreased metabolism of ALA to EPA and DHA [73]. Consumption of n-3 as ALA does contribute to a more favorable n-6:n-3 ratio as part of the overall background diet. Fish, however, is a direct source of the preformed n-3 EPA and DHA, which are more efficient at providing their high-level anti-inflammatory and proresolving actions [74,75].

There are myriad options with respect to n-3 LC PUFA-rich fish oil products accessible to the health care provider and/or the patient. However, many ω-3 supplements available on the market today are ethyl ester (EE) fish oil supplements, whose structural difference from natural triglycerides results in functional limitations to the absorption of essential n-3 FAs. The ethyl esterified FAs, ethyl-EPA and ethyl-DHA, are created by a simple transesterification (alcohol plus free
FA [FFA] after the glycerol has been removed) through mixing ethanol with the FFAs to create the ethyl esterified-EPA or DHA. This does not occur naturally in the human diet because the majority of FAs consumed are in the form of a glyceride. The glycerol backbone is the normal, physiologic “alcohol” that is esterified with the FFA [76,77]. The oxidation kinetics of DHA as an EE or as a triglyceride were assessed by measuring the concentration of oxygen found in the head space of a reaction vessel with both triglyceride and EE forms [78]. The EE form of DHA was more reactive and quickly oxidized, which demonstrates that EEs are far less stable and can more readily produce harmful oxidation products. Furthermore, the stability of phospholipids, triglycerides, and EEs that contain DHA has been assessed [64]. After a 10-week oxidation period, the EE-DHA oil decayed 33% more rapidly than the triglyceride form of DHA [64].

Dietary fish oil (triglycerides) is digested in the small intestine by the emulsifying action of bile salts and the hydrolytic activity of pancreatic lipase. The hydrolysis of a TAG molecule produces 2 FFAs and a monoglyceride (1 FA combined to glycerol). These metabolic products are then absorbed by intestinal enterocytes and reassembled again as TAGs. Chylomicrons then transport the TAGs into the lymphatic channels (lacteals) and finally into the blood [79]. The digestion of EEs is slightly different due to the lack of a glycerol backbone. In the small intestine, it again is the pancreatic lipase that hydrolyzes the FAs from the ethanol backbone. However, the EE-bound FA is several-fold more resistant to pancreatic lipase compared with hydrolysis of glycerol-bound (TAG) FAs. Although EEs that are hydrolyzed produce FFA plus ethanol, it is a physiologically insignificant amount and would have negligible impact on hepatic metabolism [80]. The FFAs are taken up by the enterocytes and must be reconverted to TAGs to be transported in the blood. The TAG form of fish oil contains its own monoglyceride substrate, whereas, EE fish oil must obtain a glycerol substrate from another source. Without a glycerol or monoglyceride substrate, TAG resynthesis is delayed, which suggests that bioavailability is superior in natural TAG fish oils in comparison with EEs [81,82]. Furthermore, although speculative, this delay in TAG resynthesis in EE fish oils, coupled with the need to rebuild a TAG by finding a glycerol backbone moiety from an existing molecule, which subsequently tries to replace its backbone in the same manner, creates a competitive process that may increase free radical activity and oxidative stress.

While comparing incorporation of EPA into plasma triglyceride levels when administered as EEs versus natural triglyceride, or as FFAs, results of a number of studies have shown a noticeable delay and reduced incorporation of EPA with EE FAs from fish oil [83], yet other studies reported no difference in EPA and DHA absorption between EEs and triglycerides [84,85]. However, it is important to note that these studies used exceptionally large amounts of fish oil (28 g) to study bioavailability and may not accurately reflect true absorption capacity for EPA and DHA because people typically take approximately 500 mg, an amount 56 times smaller than that studied [83]. Moreover, discrepancies in bioavailability may be explained by intake differences when combined with different types of meals. For example, when supplements were given as part of a lipid-rich meal, investigators found similar rates of ω-3 from EEs and triglycerides [85,86]. When taken without a high-fat meal, Lawson and Hughes [86] reported that only 20% of ω-3 in the EE was absorbed. The findings appear to suggest that assimilation of EPA and DHA administered as EE may be enhanced when given as part of high-fat meals [86]. This effect appears to be lost when subjects are instructed to take their supplement capsules when eating meals without excessive fat, which results in clearly higher bioavailability of TAG [81].

More recently, the superior bioavailability of TAG versus EE form of fish oil has been somewhat clarified by a well-designed, double-blind, and placebo-controlled study assessing the enrichment of EPA and DHA in plasma triglycerides, cholesterol esters, and phospholipids, administered for 2 weeks as cod liver oil, fish oil, EEs, FFAs, and re-esterified triglycerides [81]. Another recent well-designed study compared the bioavailability of a moderate dose of n-3 FA as TAG to n-3 FA-EE as part of a 6-month randomized controlled study. In this study, the ω-3 index, the percentage of EPA plus DHA in red blood cell membranes, which reflects the long-term intake and ω-3 FA status of an individual [87], was found to increase to a greater extent when identical doses of EPA and DHA were consumed as TAGs versus EEs [81].

A Beneficial n-6 PUFA: γ-Linolenic Acid

An essential FA, γ-LA (GLA) (18:3 n-6), is found in certain plant-seed oils, including borage-seed oil. GLA is metabolized to dihomogamma LA (DGLA) (20:3 ω-6), for which there is a preferential shunt pathway to generate PGE1, an eicosanoid with anti-inflammatory and immunoregulatory properties [88]. In addition, GLA cannot be enzymatically converted to inflammatory leukotrienes by 5-LOX due to its unique chemical structure. Instead, it is converted to 15-hydroxy-DGLA, which has the additional beneficial action of suppressing 5-LOX activity [89]. GLA and DGLA also modulate immune responses independently of eicosanoids by acting directly on T lymphocytes [90]. Finally, GLA has been shown to suppress acute and chronic inflammation, including arthritis, in animal models [91].

Nutrition for Weight Loss and Body Composition

Weight loss is a priority for long-term management of OA, which leads to reduced arthrokineamatic stress loads and
improved functional status with greater standing tolerance and ambulatory and work capacity [92,93]. Retaining fat-free mass with weight loss and increasing skeletal muscle strength and function has been shown to improve functional capacity in individuals with OA [94,95]. The link with overweight, obesity, and OA extends beyond biomechanical stress to include metabolic, neuroendocrine, and epigenetic factors. Physiologic adipocytokine concentrations can be achieved via diet, exercise, and weight loss, which makes long-term body composition a modifiable risk factor [96]. A thorough review of the literature concerning the influence of energy balance and macronutrient manipulation in weight management and lean body mass retention with fat loss is beyond the scope of this article. Clearly, the fundamental principle for effective and sustained weight loss is to induce a caloric deficit via diet and/or physical activity. However, there is an established body of evidence that demonstrates that, by displacing a portion of dietary carbohydrate (particularly, starchy and high glycemic index and/or insulinogenic carbohydrates) for dietary protein and fibrous carbohydrates (ie, fibrous vegetables and fruits), while maintaining adequate essential FA consumption will optimize cardiometabolic health and changes in body composition [97-100]. Sköldstam et al [101] showed the Mediterranean diet to improve multiple measures in functional status, quality of life, and inflammation over 12 weeks in a cohort of patients with active RA. The impressive body of evidence that supports the Mediterranean diet for primary and secondary prevention of cardiovascular disease, metabolic disease and/or diabetes, obesity, and certain cancers makes it an ideal fundamental diet to modify for enhancing its potential benefits in OA [102]. Its benefits are largely attributed to the predominance of n-3 FAs and the presence of anti-inflammatory phytochemicals from extra virgin olive oil, fruits, and vegetables. Furthermore, n-3 HUFA supplementation in the form of fish oil has been shown to increase skeletal muscle protein synthesis in older adults, in addition to enhancing the effects of strength training in elderly women, which suggests a potential role for mitigating sarcopenia [60,102].

**Macronutrient and FA Dosing Considerations**

Based on a comprehensive assessment of the available evidence and benefit: risk ratio, by supplementing with a high-quality fish oil supplement that is predominantly in the TAG form, and third-party tested for purity, potency, and freshness with a total daily dose of at least 2 g and up to 4 g of EPA plus DHA, would be prudent for the purposes of both chondroprotection and synovioprotection. The fish oil may be co-supplemented with 300 mg of krill oil and 450-2000 mg of GLA from borage seed or evening primrose oil to provide additional yet potentially complementary benefits for individuals with OA or those at-risk populations that look to proactively support joint health. Dosing should depend on multiple factors such as comorbidities, allergy or sensitivities, concurrent medications, individual needs, and resources. For example, the higher dose ranges for n-3 EPA plus DHA and n-6 GLA may be considered for a patient with OA and with hypertriglyceridemia, prediabetes, metabolic syndrome with good glycemic control, coronary artery disease, and psoriasis. A modified Mediterranean background diet focused on energy intake (kcal) to maintain a healthy body weight and body fat percentage, while the macronutrient composition is based on moderate protein, moderate carbohydrate from fibrous grains, fruits, and vegetables, along with an n-6 to n-3 PUFA ratio of less than 4:1, may provide long-term nutritional support for preventing and/or managing OA.

**SUMMARY**

Maintaining a healthy body weight, lifestyle and physical activity, medical management with anti-inflammatory and analgesics by using minimally invasive and/or surgical procedures, and physical medicine and rehabilitation methods remain the more common strategies for treating and preventing OA. However, strategic nutritional intervention is emerging as an additional cost-effective tool in OA with a favorable safety profile for optimizing outcomes from traditional clinical treatment strategies. The strategic displacement of highly insulinemic carbohydrates with fibrous carbohydrates and high-quality protein, and reduction of n-6:n-3 PUFA ratio in the whole-food background diet may support optimal body composition and joint health. In addition, the use of n-3 HUFA EPA plus DHA from both purified fish oil and krill oil, along with the n-6 GLA, may provide secondary benefits for improving and supporting the health of multiple organ systems, including the cardiovascular, gastrointestinal, endocrine, renal, immune, visual, and nervous systems.

**REFERENCES**


