Fatty Acids and Rheumatoid Arthritis

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Rheumatoid arthritis (RA) is one of the most common chronic autoimmune inflammatory diseases. The prevalence of RA in the world ranges from 0.5% to 1.0%, with the predominant percentage being women. What is characteristic of RA is the appearance of pathological changes, which first occur in the joint lining. The B cells, macrophages and CD4+ helper T cells infiltrating the synovial stroma result in the spread of the synovium, which causes swelling and pain in the joints. For a long time, omega-3 FAs, especially eicosapentaenoic acid (EPA; 20: 5n-3) and docosahexaenoic acid (DHA; 22: 6n-3), have been regarded as factors with immunomodulating and anti-inflammatory properties. Although it is widely believed that omega-6 FAs have a proinflammatory effect, some data indicate their immunomodulatory potential. Therefore, the medium-chain omega-3 and omega-6 FAs ALA and LA, respectively, are essential nutrients for mammals, including humans.

nutrition fatty acids rheumatoid arthritis

1. Introduction

Rheumatoid arthritis (RA) is one of the most common chronic autoimmune inflammatory diseases. The prevalence of RA in the world ranges from 0.5% to 1.0%, with the predominant percentage being women [1]. RA causes disability in 400,000–600,000 people. The first symptoms of the disease appear between the ages of 25 and 35. The highest incidence is observed in patients between 40 and 60 years of age. RA is a systemic disease of connective tissue characterised by nonspecific, symmetrical inflammation of mainly small and medium-sized joints, extraarticular lesions and systemic complications. It has periods of remissions and exacerbations and can lead to joint destruction, deformation, contractures and impaired function and, ultimately, is the most common cause of disability, progressive disability and premature death [2].

The causes of RA are not exactly known. Up to 60% of the risk for developing RA can be attributed to environmental susceptibility factors [3], but not many of them have been identified to date [4][5]. Several factors can influence the development of the disease. Some of them are disorders of the acquired immune response—they participate in the initiation and maintenance of disease development, with a special role of T lymphocytes recognising the body's own antigens, e.g., citrullinated autoantigens, and supporting the production of autoantibodies with the same specificity, e.g., anti-CCP antibodies. The consequence of polyclonal B cell activation and excessive humoral immune response is the production of various autoantibodies, including RF, the presence of which is found in approximately 80% of RA patients. In such cases, the disease is characterised by a more severe clinical course. Additionally, a previous infection, especially viral, translates into the stimulation of the immune system in response to infection, which, in people predisposed to RA, may trigger an autoimmune reaction directed

against the joint structures. Attention is drawn to the antigenic similarity of some bacteria or viruses and HLA-DRB1 and HLA-DRB4 histocompatibility antigens [6], often present in RA patients, which is conducive to the initiation of the autoimmune process. What is characteristic of RA is the appearance of pathological changes, which first occur in the joint lining. The B cells, macrophages and CD4+ helper T cells infiltrating the synovial stroma result in the spread of the synovium, which causes swelling and pain in the joints. In addition, the overproduction of inflammatory molecules, tumour necrosis factor (TNF), prostaglandin E2 (PGE2), interleukin (IL)-1 and cytokines induces chronic inflammation. TNF and IL-1 in particular play a significant role in the inflammatory process of joints in RA.

So far, researchers have focused mainly on the factors influencing the negative course of RA and the deterioration in the prognosis and treatment effectiveness, indicating smoking [7] and alcohol consumption [2][8] as the most important predictors. However, other modifiable risk factors for RA require further exploration. What is particularly interesting with regards to the nutritional factors is the consumption of unsaturated FAs. This is because of the role they play in the primary prevention of many chronic illnesses, including CVD diseases [9][10]. A few studies have shown that omega-3 FAs may be useful in treating some symptoms of RA [11][12], possibly through their anti-inflammatory effects [13]. For a long time, omega-3 FAs, especially eicosapentaenoic acid (EPA; 20: 5n-3) and docosahexaenoic acid (DHA; 22: 6n-3), have been regarded as factors with immunomodulating and anti-inflammatory properties [14]. Although it is widely believed that omega-6 FAs have a proinflammatory effect, some data indicate their immunomodulatory potential [15]. Therefore, the medium-chain omega-3 and omega-6 FAs ALA and LA, respectively, are essential nutrients for mammals, including humans. The relationship between polyunsaturated FA consumption and the risk of developing RA remains unclear, as the research results are inconclusive.

2. The Involvement of Fatty Acids in the Development of RA

Essential fatty acids released from phospholipids become precursors for the intrinsic synthesis of eicosanoids. These compounds include PG, prostacyclins (PGI), thromboxanes (TX) and leukotrienes. Eicosapentaenoic acid is converted to trienoic compounds (PGE3, PGI3, TXA3 and LTB5); linoleic acid is converted to monoenoic compounds (PGI1 and TXA1) and AA is a precursor to dienic compounds (PGE2, TXA2 and LTB4). Eicosanoids differ in their biological functions and, for this reason, often exhibit opposing actions. They influence, among others, the regulation of cardiovascular function, blood pressure, coagulation, plasma triglyceride levels, immune response and inflammatory processes [16]. The products of n-3 and n-6 EFA metabolism influence cellular biochemical processes; however, their different structures determine different activities; therefore, a properly balanced amount of both groups of acids in the diet is very important. Eicosanoids formed from AA already in small amounts show high biological activity and may exhibit prothrombotic and proinflammatory effects. On the other hand, eicosanoids, which are formed from n-3 EFAs, show anticoagulant, anti-inflammatory and vasodilatory effects [17][18]. An adequate supply of omega-3 fatty acids has a positive effect on reducing the production of highly proinflammatory eicosanoids (PG2, TX2 and LT4); increasing the production of weakly proinflammatory eicosanoids (PG3, TX4 and LT5); regulating the expression and activity of COX enzymes 5-LOX and the secretion of proinflammatory

cytokines TNF, IL-1 and -6; allows a more effective control of granulocyte and macrophage activity; regulates adequate levels of resolvins and protease synthesis and helps to extinguish inflammation in the body [19].

The dietary consumption of omega-3 FAs may play an important role in the aetiology of RA. In their study, Kosińska et al. [20] found that polyunsaturated FAs constitute 13.5% of all FAs in the synovial fluid of patients with osteoporosis and RA, and the composition of the synovial fluid does not depend on the patient's age. Similarly, a study by de Pablo et al. [21] revealed a significant relationship between the level of LA and preRA (OR 0.29; 95% CI 0.12–0.75) and the risk of developing RA. However, there was no association with other omega-3 or omega-6 FAs. In a study by Di Giuseppe et al. [22], dietary omega-3 FAs consumption exceeding 0.21 g/d was associated with a 35% decrease in the risk of developing RA ((RR) 0.65; 95% CI 0.48–0.90), as compared with a lower consumption of these fatty acids. However, long-term consumption greater than 0.21 g/d was associated with a 52% reduced risk of developing RA (95% CI 29–67%).

According to the available studies, polyunsaturated long-chain FAs may have prophylactic properties in the formation of RA. In their study, Gan et al. [23] assessed the relationship between the use of omega-3 FA supplements and the content of omega-3 FAs in RBC membranes, as well as the formation of anti-CCP autoantibodies in a population free of RA yet genetically predisposed to this disease. Positive anti-CCP2 antibodies were found in 30 patients, and 47 with negative autoantibody results qualified for the study. The likelihood of developing anti-CCP2 was inversely proportional to the total omega-3 FA content in the RBC (OR: 0.47; 95% CI: 0.24–0.92, for the s.d. increase), suggesting that omega-3 FAs may have a protective effect against developing RA in its preclinical stage.

A study conducted by Rodriguez-Carrio et al. [24] demonstrated lower levels of palmitoleic, palmitic, arachidonic, oleic, EPA and DHA acids in RA patients. These patients had an overrepresented NEFA profile, characterised by an increased content of stearic acid and a decreased content of EPA and DHA, as compared to healthy controls (p = 0.002). This was associated with clinical features (RF, erosions and shared epitope); increased expression of IFNγ in CD4+ T cells (p = 0.002) and serum environment enriched for Th1 (IFNγ, CXCL10 and CCL2, $p < 0.005$). These authors conducted in vitro tests that showed that an imbalance between FAs may be the cause of IFNγ production by CD4+ T cells. The clinical response to the blockade of TNF-α had an effect on the NEFA-level changes. Thus, the clinical features of the aggressive form of RA and an increased response of Th1 cells are associated with a changed NEFA profile in patients with RA.

The available studies have shown that supplementation with omega-3 FAs may be associated with the risk of developing RA [25][26][27][28][29]. In an observational study by Rosell et al. [26], the consumption of fatty fish was associated with a moderately reduced risk of developing rheumatoid arthritis (OR 0.8 (95% confidence interval = 0.6–1.0)). In the Pedersen et al. study [27], an increase in the intake of 30 g/d of fatty fish (≥8 g fat/100 g fish) was associated with a 49% reduction in the risk of developing RA (p = 0.06), whereas the intake of medium-fat fish (3–7 g fat/100 g fish) was associated with a significantly increased risk of developing RA. Additionally, the frequency of fish consumption had an effect on the development of RA. Shapiro et al. [29] demonstrated that the consumption of cooked or baked fish was associated with a reduced risk of rheumatoid arthritis, and this risk was significantly

lower when >1 serving per week was consumed compared with 1 serving. Similarly, the consumption of olive oil or cooked vegetables significantly reduced the risk of RA (OR: 0.38 and 0.24, respectively) [28]. In the study by Lee and Park [25], the levels of ALA, EPA and omega-3 index (EPA + DHA) in erythrocytes were significantly lower in RA patients than in the controls. A regression analysis showed that the levels of ALA and EPA and the ratio of EPA to AA were negatively associated with RA risk. The PGE2 concentration was significantly decreased, with an increased DHA concentration in the erythrocytes of RA patients.

3. The Role of Fatty Acids in the Treatment of RA

A few studies have shown that omega-3 FAs may be useful in treating some of the RA symptoms [11][12], possibly through their anti-inflammatory effects [13]. For a long time, omega-3FAs, especially EPA (20: 5n-3) and DHA (22: 6n-3), have been regarded as factors with immunomodulating and anti-inflammatory properties [14]. In a study by Proudman et al. [30], the impact of unsaturated FA consumption (omega-3, eicosapentaenoic acid and docosahexaenoic acid) on the outcome of patients treated for RA was confirmed. The study included patients with RA lasting <12 months who were DMARD-naïve and randomised to a high-dose fish oil group (5.5 g/d) or a low-dose fish oil group (0.4 g/d for masking the purpose). The trial assessed the failure of a triple therapy with disease-modifying antirheumatic drugs (DMARD). The high-dose EFA group displayed a significantly lower failure of triple DMARD therapy (HR 95% CI 0.10–0.54; p = 0.0006) after adjusting for smoking history, baseline anti-CCP and shared epitope. This group of patients was also characterised by a significantly higher rate of remission according to ACR as compared to the control group (HRs = 2.09 (95% CI 1.02–4.30; p = 0.04) adjusted).

A study by Gan et al. [31] analysed the relationship between RF, anti-CCP2 Ab and the percentage of omega-3 FAs in RBC membranes, as well as the relationship between the reported use of omega-3 FA supplements and the incidence of anti-CCP2 Ab and RF. It was shown that there was an inverse association between the increase in omega-3 FA% in RBC and RF in participants who displayed shared epitope positivity (OR 0.27, 95% CI 0.10–0.79). No such association was observed in shared epitope negative participants. There were similar associations with anti-CCP positivity in SE-positive participants (OR 0.42, 95% CI 0.20–0.89). However, no such relationships were observed in SE-negative participants. In the SERA cohort, there was an association between the use of n-3 FA supplements and a lower incidence of RF positivity in SE-positive participants at the baseline (OR 0.32, 95% CI 0.12–0.82). There was no such relationship in shared epitope-negative participants. Similar trends were observed with anti-CCP2; however, they were not significant. Thus, n-3 FAs may have a potential protective influence on autoimmunity associated with RA, which is most evident in individuals who are genetically susceptible to RA in HLA class II.

Jeffery et al. [32] in their study showed that the concentration of PC EPA is associated with the clinical improvement of anti-TNF therapy in vivo and prevents the influence of ETN on Th17 cells in vitro. Thus, EPA supplementation may be an easy way to improve the outcomes of anti-TNF treatment in RA patients through Th17 frequency suppression. On the other hand, Beyer et al. [33] showed that there was an association between seafood consumption and a better outcome in RA treatment. These authors found a correlation between the omega-3 index >8, observed in 14% of patients, and higher VAS scores (p = 0.004) assessing the patient's global health.

The effects of pharmacological treatment on the disease activity in RA may be complemented by including mussels in the patient's diet. Such an addition can also contribute to the reduction of fatigue and pain in RA patients. In a study by Lindqvist [34], patients on a blue mussel diet had lower CRP, fewer tender joints, significantly improved global health and reduced pain and fatigue. In another study by Lindqvist [35], changes in the increase of omega-3 FAs EPA and DHA were observed in a group of patients who consumed blue mussels. In a study by Barebring et al. [36], a diet rich in fish, crustaceans, fruit and vegetables and whole grains was associated with a reduction in ESR (B = −2.4, $p = 0.002$) and hs-CRP (B = −0.6, $p = 0.044$). However, it was not associated with disease activity (DAS-28).

A study by Fu et al. [37] demonstrated a significant difference in the clinical disease activity index (CDAI) and disease activity scale (DAS28) after a 6-month intervention with the use of hard-shelled mussel lipid extract (Mytilus coruscus). Furthermore, there was a significant decrease in interleukin (IL)-1β, PGE2 and TNF-α but not IL-6 in this patient group and a significant increase in IL-10, indicating the potential of hard-shelled mussels as an adjunct to rheumatoid arthritis.

In another study [38], the patients with RA were divided into two food groups. In the first one, their food was enriched with Schizochytrium sp. microalgae oil (2.1 g DHA/d) and, in the second, with sunflower oil (placebo). The participants consumed the foods for 10 weeks (crossover). During this time, they maintained their regular intake of RA medications. The daily consumption of DHA reduced the sum of swollen and tender joints (66/68) from 13.9 ± 7.4 to 9.9 ± 7.0 ($p = 0.010$) and the total DAS28 index from 4.3 ± 1.0 to 3.9 ± 1.2 ($p = 0.072$). On the other hand, the consumption of sunflower oil (placebo) increased the content of LA and AA in EL (erythrocyte lipids), which mainly consist of erythrocyte membranes ($p < 0.05$). Patients supplemented with DHA presented a two-fold increase in the amount of DHA in the EL, and their AA/EPA and AA/DHA ratios were significantly reduced. These authors observed a significant reduction in the concentration of thromboxane B2 derived from AA and the ability of the blood to convert AA into 5-hydroxyeicosatetraenoic acid, which is a proinflammatory 5-lipoxygenase product. On the other hand, there was a significant increase in the levels of maresin/resolvin precursors derived from DHA and 14-/17-hydroxydocosahexaenoic acid as the result of DHA supplementation. Therefore, it can be concluded that DHA supplementation from microalgae reduces disease activity in RA patients, along with shifting the balance of lipid mediators derived from AA and DHA towards the anti-inflammatory/proliferative state.

In a study by Beyer et al. [39], the total concentration of FAs was higher in patients with active RA than in those in remission ($p = 0.047$). Similarly, RA patients treated with prednisolone had a higher total concentration of FAs as compared to those who did not receive prednisolone ($p = 0.043$). Although several single FAs varied with regards to the activity status of RA disease, prednisolone treatment or periodontal status, only C15:0 showed a positive association with CRP ($p < 0.01$, R = 0.30).

The Mustonem study [40] analysed the composition of infrapatellar fat pad (IFP) and synovial fluid (SF) from the knees of patients with RA and OA who had total joint replacement surgery. Joint diseases caused a significant decrease in the share of omega-6 FAs in the synovial fluid of OA and RA patients. The share of total MUFAs increased in SF in both RA and OA patients. As for IFP, the shares of 20: 4n-6, total omega-6 FA and 22: 6n-3 were

lower in patients with RA. They also had a lower omega-3 FA product/precursor ratio compared to OA patients. The complex changes in FA signatures could contribute to the inflammatory processes and the destruction of cartilage in the knees of OA and RA patients, but they could also limit them. In contrast, in a study by Nasriati et al. [41], no correlation was found between FFA and the levels of TNF-α and the levels of VCAM-1 in RA patients. However, there was a negative correlation between the level of FFA and the level of VCAM-1 in RA patients.

Differences in the perception of clinical improvement after the introduction of dietary PUFAs may be due to the presence of specific genetic variants altering the ability of individuals to convert dietary MC-PUFAs to LC-PUFAs. In recent years, there has been a growing number of studies demonstrating population differences in the metabolic efficiency of the PUFA pathway due to genetic variants in fatty acid desaturase genes (FADS). Some studies have indicated that the FADS1 (Δ5-desaturase) step of PUFA biosynthesis appears to be the most genetically regulated step of PUFA biosynthesis in humans. However, most studies in the field have pointed to the FADS2 (Δ-6 desaturase) step as a critical step limiting the post-synthesis of LC-PUFAs such as AA, EPA and DHA [42][43]. Furthermore, different fatty acids in the diet (from heterogeneous diets) can affect several points in the biosynthetic pathway. Some PUFAs serve as enzymatic substrates for steps early in the pathway, whereas others serve as product inhibitors for the same enzymatic steps. High concentrations of LC-PUFAs, such as AA (derived from the conversion of LA to AA), may then affect the levels of proinflammatory eicosanoids, which, in turn, appear to be associated with elevated markers of low-level systemic inflammation, such as CRP, and increase the risk of diseases such as atherosclerosis [44][45]. To date, this hypothesis has been tested in heterogeneous human populations that also have high interindividual variability in the dietary concentrations of MC- and LC-PUFAs and in populations that are typically established by specific proinflammatory clinical conditions [46].

The supplementation of omega-3 FAs may support RA therapy. Das Gupta et al. [47], in their study, gave patients indomethacin (75 mg/d) or indomethacin (75 mg/d) and omega-3 FAs (3 g/d) over 12 weeks. Both groups showed moderate improvement in disease activity after 12 weeks of treatment. Physical functioning, physical role, body pain, general health, vitality, social functioning, grip strength and duration of morning stiffness improved significantly in the combination group compared with the indomethacin-only treatment group.

In the study by Aryaeian et al. [48], the group taking CLAs and vitamin E at the above doses had significantly lower ESR levels and significantly lower white blood cell counts compared to the placebo group. In addition, CLA supplementation reduces the SBP levels and mean arterial pressure and decreases the erythrocyte sedimentation rate of RA patients [49]. In the study by Ormseth et al. [50], the serum FFAs levels were associated with the HOMA-IR ($p = 0.011$), CRP ($p = 0.01$), triglycerides ($p = 0.005$) and Framingham risk scores ($p = 0.048$).

The use of an anti-inflammatory diet containing fish oil significantly reduces the number of tender and swollen joints and duration of morning stiffness of RA patients [51][52][53][54][55][56][57][58][59][60][61][62][63][64][65][66][67][68][69][47][70][71]. In a study by Adam O et al. [65], a fish oil diet resulted in greater EPA enrichment in erythrocyte lipids (244% vs. 217%) and less formation of leukotriene B (4) (34% vs. 8%, $p > 0.01$), 11-dehydro-thromboxane B (2) (15% vs. 10%, $p < 0.05$) and prostaglandin metabolites (21% vs. 16%, $p < 0.003$). In contrast, a diet low in AA alleviated the clinical signs of inflammation in RA patients and potentiated the beneficial effects of fish oil supplementation.

Additionally, in a study by Kremer et al. [61], as a result of EPA and DHA supplementation, leukotriene B4 production by neutrophils decreased by 19 to 20% and interleukin-1 production by macrophages by 40.6–54.7% after 24 weeks. In a study conducted on 50 patients with RA, dietary supplementation with fish oil containing 60% omega-3 FAs resulted in a significant increase in the plasma EPA and monocyte lipid levels and clinical improvement in the study group [53]. In a study by Cleland et al. [66], after 12 weeks, the fish oil treatment group showed an improvement in the tender joint scores and grip strength, a reduction in the mean duration of morning stiffness, a reduction in pain and a 30% reduction in leukotriene B4 production by isolated neutrophils stimulated in vitro. Gruenwald et al. [70], in addition to a reduction in the duration of morning stiffness and a reduction in the number of painful and swollen joints at 6 and 12 weeks post-study, observed a 60% reduction in pain among patients taking EPA and DHA in the form of fish oil concentrate.

In the studies analysed, taking omega-3 FAs resulted in taking significantly less analgesic and antirheumatic preparations [52][72][73][59][74][75][76]. In the study by Lau et al. [73], this effect reached a maximum at month 12 and persisted until month 15. However, no change in the clinical and laboratory parameters of RA activity was observed in association with reduced NSAID consumption. Similarly, in a study by Brzeski et al. [74], patients taking GLA-rich evening primrose oil reduced the dose of NSAIDs and achieved clinical improvement. Additionally, GLA-rich borage seed oil significantly reduced the signs and symptoms of disease activity in patients with rheumatoid arthritis ($p < 0.05$) [57]. An overall clinical response (significant GLA administration) reduces joint inflammation in patients with rheumatoid arthritis by inhibiting IL-1 beta release from LPS-stimulated human monocytes [77]. GLA induces a protein that reduces the stability of pro-IL-1 beta mRNA. IL-1 beta is important for the host defence, but the enhancement mechanism may be excessive in genetically predisposed patients. The reduction of IL-1 beta autoinduction may therefore be protective in some patients with endotoxic shock and diseases characterised by chronic inflammation [78][77]. Belch et al. [76] observed significant improvement and reduction in NSAID use in groups using EPO and EPO with fish oil for 12 months. Moreover, the discontinuation of supplementation resulted in functional deterioration after 3 months in those receiving active treatment. Geusens et al. [72] found that patients taking 2.6 g/d of omega-3 FAs achieved significant improvements in patient global assessment and pain and reduction in antirheumatic medication. In the study by Galarraga et al. [52] of 49 patients, 19 (39%) in the cod liver oil group and five (10%) in the placebo group were able to reduce their daily NSAID requirements by >30%. There were no differences between the groups in the clinical parameters of RA disease activity or in the observed side effects.

In addition to the perceived subjective change in the clinical condition of RA patients after taking omega-3 FAs, researchers also observed changes at the biochemical level in the bodies of the patients studied [79][80][81][75][82][83]. In a study by Dawczynski et al. [80], in the group taking FAs (1.1 g a-linolenic acid, 0–7 g EPA and 0.1 g DPA and 0.4 g DHA and 50 mg/d AA), it was found that omega-3 FAs inhibited the immune response by significantly reducing the number of lymphocytes and monocytes. Omega-3FAs did not increase the oxidative stress biomarkers, such as 8-iso-PGF(2alpha) and 15-keto-dihydro PGF(2alpha), and DNA damage, such as 7,8-dihydro-8-oxo-2′-deoxyguanosine. In a study by Espersen et al. [81], the plasma interleukin-1 beta levels were significantly reduced in the study group after 12 weeks ($p < 0.03$) of taking 3.6 g/d omega-3 FAs. The anti-inflammatory effect of fish oil was also demonstrated in a study by Sperling et al. [82]. After fish oil supplementation, the AA:EPA ratio in

neutrophil cell lipids decreased from 81:1 to 2.7:1, and the mean leukotriene B4 production decreased by 33%. There was also a 37% decrease in platelet-activating factor production at week 6. In a study by Cleland et al. [75], after 3 years of fish oil use, AA was 30% lower in the platelets and 40% lower in peripheral blood mononuclear cells in subjects taking fish oil. Serum thromboxane B2 was 35% lower, and whole-blood PGE2 stimulated by lipopolysaccharide was 41% lower with fish oil consumption compared with no fish oil. In a study by Kolahi et al. [79], in the fish oil supplementation group (1 g/d), the osteoprotegerin levels increased, while sRANKL, TNF-alpha and the sRANKL/osteoprotegerin ratio decreased, and there was a significant positive correlation between the sRANKL/osteoprotegerin ratio and TNF-alpha levels ($r = 0.327$, $p = 0.040$). The literature data suggest the involvement of the potent chemotactic factors 5-HETE and leukotriene B4 in inflammatory disease in humans [83]. A study of synovial fluid from patients with RA, spondyloarthropathy (SA) or noninflammatory arthropathy (NIA) showed that 5(S),12(R)-dihydroxy-6,8,10-(trans/trans/cis)-14-cis-eicosatetraenoic acid (leukotriene B4) in synovial fluid was significantly elevated in patients with RA and the rheumatoid factor present ($p < 0.05$, $n = 14$) and in patients with SA ($p < 0.05$, $n = 10$) compared with those with NIA ($n = 9$) [83]. The content of 5(S)-hydroxy-6,8,11,14-eicosatetraenoic acid (5-HETE), but not leukotriene B4, was significantly elevated in the synovial tissue of seven RA patients compared with four NIA subjects ($p < 0.05$). A single intraarticular corticosteroid injection significantly decreased the leukotriene B4 levels in the synovial fluid of six RA patients [83]. In the study by Bae et al. [84], there were no significant differences in the proinflammatory cytokines, CRP levels and disease severity in the groups taking quercetin with vitamin C (166 mg + 133 mg/capsule) and alpha-lipoic acid (300 mg/capsule). In the study by Dawczynski et al. [85], following the administration of 3 g/d omega-3 FAs, the AA/EPA ratio decreased from 6.5 ± 3.7 to 2.7 ± 2.1 in the plasma lipids and from 25.1 ± 10.1 to 7.2 ± 4.7 in the erythrocyte membranes ($p \leq 0.001$). In the group taking GLA and in the group taking omega-3 FAs and GLA simultaneously, there was a strong increase in the GLA and dihomo-γ-linolenic acid concentrations in the plasma lipids, cholesterol esters and erythrocyte membranes. Jäntti et al. [86] showed that the decrease in EPA and increase in AA serum concentrations induced by evening primrose oil may not be beneficial in patients with rheumatoid arthritis in light of the role of these FAs as eicosanoid precursors. Decreases in essential FAs are associated with increased desaturase/elongation enzyme activity, increased eicosanoid production or metabolic changes secondary to a cytokine-mediated inflammatory response [87]. In a study by Fraser et al. [88] evaluating how changes in FFAs after a 7-day fast in rheumatoid arthritis (RA) patients will inhibit T-lymphocyte proliferation in vitro, it was demonstrated that both the concentration of the FFA mixture and the ratio of unsaturated and saturated fatty acids significantly affected lymphocyte proliferation in vitro ($p < 0.0001$).

The three studies reviewed did not show an association between omega-3 FAs intake and subjective clinical improvement [89][90][91]. In the study by Remans et al. [89], patients in the study group supplementing EPA, DHA, GLA and micronutrients showed a significant increase in the plasma levels of vitamin E ($p = 0.015$) and EPA, DHA and docosapentaenoic acid, with a decrease in the AA levels ($p = 0.01$). Similarly, in the study by Sundrarjun et al. [90], patients consuming foods low in omega-6 FAs and supplemented with omega-3 FAs at week 18 had significantly decreased linoleic acid, CRP and sTNF-R p55 concentrations and significant increases in EPA and DHA compared to the placebo group. At week 24, there was a significant reduction in the interleukin-6 and TNF-alpha levels in the group; however, no association with clinical improvement in the patients was observed. In the

study by Haugen et al. [91], the 20: 3n-6 and 20: 4n-6 fatty acid concentrations were significantly reduced after 3.5 months on a vegan diet ($p < 0.0001$ and $p < 0.01$, respectively), but the concentrations increased to the baseline values with a lactovegetarian diet. The 20: 5n-3 concentration was significantly reduced after a vegan diet ($p < 0.0001$) and a lactovegetarian diet ($p < 0.01$).

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