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Review article

Polyunsaturated omega-3 fatty acids and systemic lupus erythematosus: what do we know?☆

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ABSTRACT

Various studies have demonstrated the impact of omega-3 fatty acids on the concentration of C reactive protein (CRP), pro-inflammatory eicosanoids, cytokines, chemokines and other inflammatory mediators. Therefore, the supplementation of these types of lipids may represent additional option treatment for chronic systemic diseases, such as Systemic Lupus Erythematous and other rheumatic diseases. The role of these lipids has not been well established, yet. However, it seems there is a direct relationship between its intake and the decrease of the disease clinical manifestations as well as of the inflammatory status of the patients. Thus, the aim of this manuscript is to present a thorough review on the effects of omega-3 fatty acids in patients with SLE. Bibliographic data set as the Medical Literature Analysis and Retrieval System Online (MEDLINE) and Literatura Latino-Americana e do Caribe em Ciências da Saúde (LILACS) were searched using as key words: systemic lupus erythematous (SLE), polyunsaturated fatty acids omega-3, eicosapentanoic acid (EPA), docosahexanoic acid (DHA), antioxidants and diet. Manuscripts published up to September 2013 were included. There were 43 articles related to the topic, however only 15 pertained human studies, with three review articles and 12 clinical studies.

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Ácidos graxos poli-insaturados ômega-3 e lúpus eritematoso sistêmico: o que sabemos?

Palavras-chave:
Lúpus eritematoso sistêmico (LES)
Ácidos graxos poli-insaturados ômega-3
Ácido eicosapentaenoico (EPA)
Ácido docosahexaenoico (DHA)
Antioxidantes

RESUMO

Diversos estudos têm demonstrado a habilidade dos ácidos graxos ômega-3 em reduzir as concentrações de proteína C-reativa (PCR), eicosanoides pró-inflamatórios, citocinas, quimiocinas e de outros biomarcadores da inflamação. Por essas propriedades, a suplementação com essa classe de lipídeos pode representar terapia adicional ao tratamento de doenças inflamatórias crônicas sistêmicas, como o lúpus eritematoso sistêmico (LES) e outras doenças reumáticas. O papel dessa classe de lipídeos no LES ainda não está bem estabelecido. No entanto, parece haver relação entre o consumo deste tipo de gordura e a diminuição das manifestações e da atividade inflamatória da doença. Sendo assim, este artigo apresenta revisão da literatura científica sobre os efeitos dos ácidos graxos ômega-3 em pacientes com LES. Realizou-se levantamento bibliográfico junto aos bancos de dados Medical Literature Analysis and Retrieval System Online (MEDLINE) e Literatura Latino-Americana e do Caribe em Ciências da Saúde (LILACS), utizando-se como palavras-chave: lúpus eritematoso sistêmico (LES), ácidos graxos poli-insaturados ômega-3, ácido eicosapentaenoico (EPA), ácido docosahexaenoico (DHA), antioxidantes e dieta. Foram incluídos artigos publicados até setembro de 2013. Quarenta e três artigos relacionados ao tema foram encontrados. Após limitar a busca apenas para estudos realizados em seres humanos foram encontrados 15 artigos, sendo três de revisão e 12 ensaios clínicos.

Introduction

Beneficial effects of omega-3 polyunsaturated fatty acids have been extensively studied, mostly those acting on the cardiovascular system.[1–4] Over the last few years, the interest in the role of this nutrient in reducing inflammation has grown.[5]

These fatty acids are considered essential and should be provided by the diet or from supplements. They compete with the arachidonic acid (AA), a member of the omega-6 family through the same enzymatic pathway and stimulate series 3 prostaglandins and series 5 leukotrienes, which have a lower inflammatory action than those AA-derived eicosanoids.[6]

Several studies have demonstrated that omega-3 fatty acids can reduce the concentrations of C reactive protein (CRP), proinflammatory eicosanoids, cytokines, chemokines, and other inflammatory biomarkers.[7–10] In addition, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), both members of omega-3 family, are precursors of the lipid mediators resolvins and protectins, which have anti-inflammatory and immunomodulatory characteristics.[11–13]

In view of these properties, supplements with this class of lipids might represent an additional therapy of systemic chronic inflammatory diseases, such as systemic lupus erythematosus (SLE) and other rheumatic conditions. Studies conducted in subjects with rheumatoid arthritis report an improvement in general physical evaluation, pain, morning stiffness and reduced anti-inflammatory agent use following supplementation with omega-3.[14–16]

The role of these fatty acids in SLE is not fully established yet. However, the intake of this kind of fat seems to be related to the reduction in disease manifestations and inflammatory activity.[17–25]

The authors present a literature review on the effects of omega-3 fatty acids on patients with SLE.

Method

A literature search on MEDLINE and LILACS databases was performed with the following keywords: systemic lupus erythematosus (SLE), omega-3 polyunsaturated fatty acids, eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), antioxidants, and diet. Articles published up to September 2013 were included. Forty-three articles related to the topic have been identified. After the search was limited to studies conducted in humans, 15 articles were found, with three of them being review articles and 12 clinical trials.

Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is a multisystemic autoimmune inflammatory disease with a large spectrum of manifestations that is clinically characterized by relapses and remission periods with a varying course and outcome. The disease severity ranges from mild to severe. However, complete and prolonged remission is rare.[26]

Although SLE etiology is not known, an interaction of genetic, hormonal and environmental factors are probably involved in the disease development, thus leading to a loss of cell immunoregulation balance.[27] This immune disturbance occurs through loss of tolerance to nuclear antigens, poorly regulated activation of B- and T lymphocytes and subsequent B-lymphocyte polyclonal activation, with large numbers of reactive self-antibodies being produced and immune complex being formed. The immune complexes, along with

self-antibodies, are primarily responsible for tissue lesion and organ damage.[28]

This complex process involves interaction of various cytokines, chemokines, adhesion molecules, and pattern-recognition receptors (PRRs) triggering cell activation.[29]

T lymphocytes with a TH1 functional response are stimulated by interleukin (IL)-12 to produce tumor necrosis factor alpha (TNF-), interferon gamma (IFN-), and IL-2. On the other hand, TH2 lymphocytes produce IL-4, IL-5, and IL-13 when stimulated by IL-4. A significant cytokine elevation resulting from the TH1 response is observed in the serum of patients with SLE, thus indicating a disturbance in TH1/TH2 response pattern is likely.[28] The TH17 functional response and serum levels of other cytokines, such as IL-23, IL-18, IL-21, and IL-23 are also elevated, but their role in the disease pathogenesis is still under investigation.[28] Many of these cytokines are elevated in the serum of patients with SLE and are associated with a higher disease activity or certain clinical manifestations.[29–32]

Few studies analyzed the role of nutrition in SLE pathogenesis to this moment. Omega-3 polyunsaturated fatty acids might have beneficial clinical effects on SLE because of their anti-inflammatory actions, which would warrant their use as another treatment option for the disease.[13]

Omega-3 polyunsaturated fatty acids

Fatty acids may be classified as saturated (no double bonds between individual carbon atoms) fatty acids and mono- or polyunsaturated fatty acids according to the number of double bonds in the chain. The most common saturated fatty acids in human food are: lauric, myristic, palmitic, and stearic acids (ranging from 12 to 18 carbon atoms). Unsaturated fatty acids are classified into two main categories: polyunsaturated fatty acids, represented by omega-6 fats (with main representatives being linoleic and arachidonic acids) and omega-3 fats (with main representatives being -linolenic, eicosapentaenoic [EPA], and docosahexaenoic [DHA] acids) or monounsaturated fatty acids, represented by the omega-9 (omega-9 – oleic) fats. Omega-3 and omega-6 fatty acids are considered essential, as they are not synthesized by the human body. The linoleic acid (18:2 omega-3) is the precursor of the other polyunsaturated fatty acids in omega-6 fats, which has soy, corn, and sunflower vegetable oils as their main food sources. In the omega-3 family, the -linolenic acid (18:3 omega-3) is found in a number of vegetables, such as canola and linseed, whereas EPA (20:5 omega-3) and DHA (22:6 omega-3) are found in deep sea cold water fish (mackerel, sardines, salmon, herring). On the other hand, oleic acid (18:1 omega-9) can be synthesized by the body and its main diet sources are olive oil, canola oil, olives, avocado and nuts (peanuts, chestnuts, walnuts, almonds).[33]

Mechanisms of action of omega-3 fatty acids

The first data suggesting a possible anti-inflammatory role for omega-3 fatty acids are derived from an epidemiological study in Greenland Eskimos conducted by Kronmann and Green in 1980. The authors found that the prevalence of diseases with an inflammatory component, such as acute myocardium infarction, diabetes mellitus (DM), multiple sclerosis, bronchial asthma, and thyrotoxicosis, was lower in the study population than in Western country populations. Eskimos diet have a large amount of seafood, which is a source of polyunsaturated fatty acids.[34] Thereafter, several studies were conducted to find the role of these lipids in many chronic diseases in which inflammation plays a major pathogenetic role.

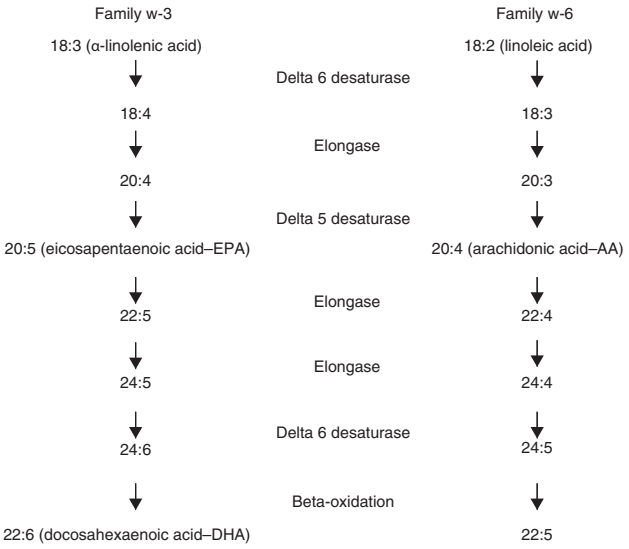

Figure 1 – Omega-3 and omega-6 fatty-acid metabolism Adapted from Leonard *et al.*, 2004.[37].

The omega-3 and omega-6 families, through their members EPA, DHA, and arachidonic acid (AA), are the essential lipid classes for eicosanoid synthesis. Eicosanoids are among the major inflammation mediators and regulators. They include prostaglandins (PG), leukotrienes (LT), thromboxanes, and other oxidized derivatives. They are produced by oxidative pathways of the enzymes cyclooxygenase (COX) and lipoxygenase (LOX).[35]

Due to their molecular similarity, linoleic acid and -linolenic acid compete for the same enzymes to synthesize derivatives with 20 carbon atoms: AA (20:4 omega-6), eicosapentaenoic acid (EPA) (20:5 omega-3) e eicosatrienoic acid (ETA) (20:3 omega-9). The -linolenic acid has a 22-carbon atom derivative, the docosahexaenoic acid (DHA) (22:6 omega-3)[33,36,37] (Fig. 1).

A high intake of linoleic acid favors an increased AA content in membrane phospholipids, thus increasing the production of series 2 and 4 eicosanoids (prostaglandin E2 and leukotriene B4) through cyclooxygenase and lipoxygenase enzymatic pathways, respectively. A high production of eicosanoids is related to the occurrence of immune disorders, cardiovascular and inflammatory diseases. On the other hand, the intake of omega-3 family fatty acids, such as -linolenic acid, EPA or DHA, which compete with AA for the same enzymatic pathways, competitively inhibits the arachidonic acid oxidation by cyclooxygenase (COX) into prostaglandins and their conversion into leukotrienes (LTs) via 5-lipoxygenase (LOX) pathway.[6,33] The omega-6 fatty acid leads to proinflammatory series 2 and 4 eicosanoid production [PGE2, thromboxane A2 (TXA2) and leukotriene B4

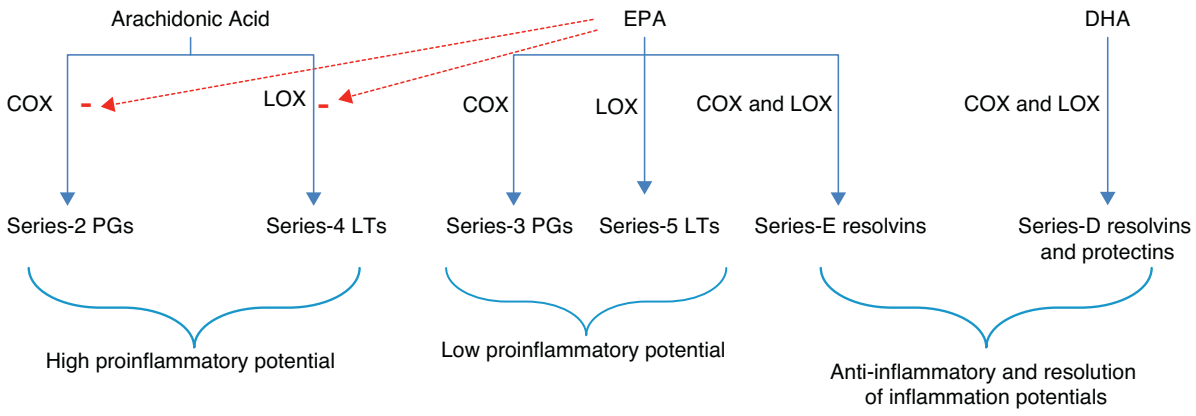

Figure 2 – Syntheses and actions of lipid mediators produced by AA, EPA, and DHA
AA, arachidonic acid; EPA, eicosapentaenoic acid; DHA, docoxahexaenoic acid; COX, cyclooxygenase; LOX, lipoxygenase; PG, prostaglandins; LT, leukotrienes
Adapted from Calder *et al.*, 2010.[13].

(LTB4)]. PGE2 induces a number of proinflammatory effects, such as increased vascular permeability, vasodilation, hyperemia, and hiperalgesia.[38–40] TXA2 promotes the synthesis of inflammatory cytokines, IL-1β and TNF-α by mononuclear phagocytes.[39,41] On the other hand, LTB_4, in addition to causing increased vascular permeability and hyperemia, is a powerful leukocyte chemotactic agent inducing the production of lysosomal enzymes and increasing the production of reactive oxygen species and cytokines, such as TNF-, IL-1, and IL-6 (Fig. 2).[39,40]

Thus, the omega-3 fatty acid acts by reducing the formation of eicosanoids with inflammatory characteristics, since it competes with omega-6 fatty acids for the same enzymatic pathway, leading to the inhibition of TNF-, IL-1 and IL-6 synthesis and reducing the intercellular adhesion molecule-1 (ICAM-1) expression.[42] It is also a substrate for the synthesis of series 3 and 5 eicosanoids, which have less inflammatory characteristics (Fig. 2).[6]

Studies in cultured cells have further demonstrated that EPA and DHA can inhibit the production of classic inflammatory cytokines, such as TNF-, IL-1, IL-6, and others.[40,43–45] In healthy subjects, reduced production of TNF-, IL-1 and IL6 by monocytes and mononuclear cells has already been demonstrated following fish oil supplementation,[9,10,46] although other studies have not confirmed those findings.[8,47,48] These differences might have occurred because of the different doses used, the duration of treatment, and non-representative samples.

T-cell proliferation inhibition and IL-2 production were also found in cultured cells following supplementation with EPA and DHA.[49] However, these findings are inconsistent in human studies.

In addition, EPA and DHA are precursors of the lipid mediators resolvins and protectins. The pathway for production of theses mediators also involves the enzymes cyclooxygenase and lipoxygenase (Fig. 2). In cultured-cell and animal studies, both resolvins and protectins demonstrated to have anti-inflammatory and immunomodulating actions.[11–13,50] Resolvins E1 and D1 and protectin D1 can inhibit neutrophil transendothelial migration, thus preventing the infiltration of immune cells at the inflammation site. Resolvin E1 can further inhibit IL-1 production and protectin E1 inhibits IL-1 and TNF- production.[50] Thus, these lipid mediators can play a role in the resolution phase of inflammation and in limiting tissue damage.

Thus, the ratio between daily intake of omega-6 and omega-3 fatty-acid sources assumes great importance in human nutrition.[36] However, the Western diet is characterized by a high omega-6 polyunsaturated fatty acid intake and high omega-6/omega-3 ratio, which favors pathogenesis in a number of conditions, including cardiovascular, inflammatory, and autoimmune diseases, as well as cancer. The omega-6/omega-3 ratio in Western diet is estimated to be 15-20:1. On the other hand, an increased omega-3 intake and a reduced ratio between these fatty acids as a consequence seems to exert a suppressive effect on disease pathogenesis.[51]

Omega-3 and Systemic Lupus Erythematosus

Few studies investigating omega-3 fatty acid effects on subjects with SLE have been conducted to this moment. However, a few trials suggest that supplementation with this class of lipids can represent an additional therapy to the standard pharmacological treatment of this disease due to their anti-inflammatory properties.[17–25]

A difference in erythrocyte and plasma fatty acid level between individuals with SLE and individuals without SLE seems to exist. However, it is not known whether this difference occurs due to an inappropriate diet or the disease itself. Aghdassi *et al.* (2011) compared the content of red cell and plasma fatty acids between women with SLE and controls, between patients with SLE with or without a history of cardiovascular disease (CVD) and between patients taking or not prednisone. Lower levels of omega-3 (EPA + DHA) and EPA alone were found in red-cell membranes of individuals with SLE compared with healthy individuals. On the other hand, no significant differences for fatty acid content between patients and controls were found in plasma. In addition, patients with

SLE and a history of CVD had higher levels of plasma monounsaturated fatty acids and higher levels of omega-6 family polyunsaturated fatty acids than those without CVD. Patients taking prednisone had higher levels of omega-3 and lower AA/EPA ratios compared with those not taking prednisone. However, these differences were not statistically significant.[23]

Low levels of omega-3 could contribute to worsen the inflammation already present in these patients, thus indicating that the nutrient supplementation, on its turn, would contribute to improve the inflammatory profile and, consequently, the disease activity, as substantiated by Elkan *et al.* (2012) in a study conducted in 114 patients with SLE and 122 subjects without the disease. The authors found that higher levels of EPA and DHA in fat cells of patients with SLE were negatively associated with disease activity (measured by Systemic Lupus Erythematosus Disease Activity Index – SLEDAI) and the presence of atherosclerotic plaques. On the other hand, higher omega-6 levels were positively associated with a higher damage index (evaluated by the Systemic Lupus International Collaboration Clinics/American College of Rheumatology Damage Index – SLICC/ACR) and the presence of atherosclerotic plaques. In this study, food intake evaluation identified that subjects with SLE described a higher carbohydrate intake and a lower fiber and polyunsaturated fatty acid (omega-6 and omega-3) intake than controls. Carbohydrate intake was positively associated with the amount of omega-6 fatty acids present in adipose tissue. An association between carbohydrate, fiber, saturated and monounsaturated fatty acid intake and disease activity or damage index could not be found.[24]

The first study evaluating the effect of omega-3 fatty acids on patients with SLE taking fish oil supplementation was reported in 1989 by Clark *et al.* The authors analyzed the effects of omega-3 (EPA and DHA) on 12 subjects with SLE and nephritis and concluded that diet supplementation with fish oil can affect the mechanisms involved in inflammation and atherosclerosis. The patients were given a supplementation over five weeks with daily doses of 6 g of fish oil, followed by a period of five weeks without the supplementation and then five more weeks with 18 g of fish oil daily. A rise in EPA and DHA levels in membrane phospholipids and reduced AA incorporation were found. These changes were associated with reduced platelet aggregation and blood viscosity and with an increase in red cell flexibility. LTB4 production by neutrophils was also significantly reduced. The higher fish oil dose induced 38% reduction in triglyceride levels and a 39% reduction in VLDL-cholesterol, associated with a 28% increase in HDL-cholesterol levels. The effects on the anti-DNA antibodies title and albuminuria was not verified.[17]

On the other hand, in another trial conducted by the same group of investigators, different results were found. In 21 patients with a stable lupus nephritis who were given a daily dose of 15 g fish oil or placebo containing olive oil over one year, an improvement in kidney function or in the disease activity was not found in the fish oil group compared with the placebo group. As for blood lipids, only VLDL-cholesterol and triglycerides had a significant reduction following the treatment with fish oil, whereas LDL and HDL fractions remained unchanged.[19]

Westberg *et al.* (1990) evaluated the effects of omega-3 fatty acids supplementation with capsules containing fish oil or capsules of olive oil as a placebo in 60 patients with moderately active SLE. Over the first three months, the patients receiving omega-3 supplementation had significant improvement in clinical and laboratory parameters. However, after a six-month supplementation, no differences between groups could be detected, which suggests, according to the authors, the supplement effects are short-lived.[18]

In 2004, Duffy *et al.* published another trial evaluating the effect of omega-3 supplements and/or copper in patients with SLE. Fifty-two patients were divided into four treatment groups. One of the groups was given 3 g of fish oil in capsules (EPA 540 mg + DHA 360 mg/capsule) and 3 mg of copper; the second group was given 3 g of fish oil and copper as a placebo; the third group received a supplement with 3 mg of copper and fish oil placebo; the fourth group received placebo instead of both nutrients. After a six-month supplementation, a reduced disease activity from 6.12 to 4.69 ($P < 0.05$), measured by the Systemic Lupus Activity Measure (SLAM) score, was found. The integument, neuromotor, and laboratory domains of SLAM-R were most affected by supplementation.[20]

Omega-3 beneficial effects on reducing lupus nephritis activity were evaluated by Nakamura *et al.* (2005). The authors examined the effect of daily supplementation with 1.8 g of purified EPA in six patients with lupus nephritis diagnosed by kidney biopsy. After a 3-month supplementation, reduced AA levels and increased levels of EPA in plasma phospholipids were detected, in addition to reduced urinary levels of 8-isoprostane (from 550 113 pg/mg CR to 235 49 pg/mg CR, $P = 0.02$). In the authors' opinion, these findings indicate that EPA can promote decreased oxidative stress, with consequent benefits for lupus nephritis treatment. On the other hand, when immune parameters were evaluated, no significant differences were found in anti-DNA and serum complement values after omega-3 treatment.[21]

Wright *et al.* (2008) compared the effects of daily intake of 3 g of omega-3 (1.200 mg of DHA + 1.800 mg of EPA) with placebo of olive oil in 60 patients with SLE over a 24-week period. They noted that the omega-3 supplementation in patients with SLE could not only have a therapeutic effect on the disease activity measured through the Systemic Lupus Activity Measure (SLAM-R) and British Isles Lupus Assessment Group (BILAG) indexes, but also promote improvement in endothelial function and reduced oxidative stress, thus conferring cardiovascular benefits.[22]

Recently, Bello *et al.* (2013) have published a double-blind, placebo-controlled trial in which 85 patients with SLE were randomized to receive either 3 g of omega-3 supplements or placebo. After a 12-week supplementation, no significant differences between the groups were found for disease activity, serum levels of inflammatory markers (ICAM-1, VCAM-1, and IL-6), and endothelial function. As for the lipid profile, patients receiving omega-3 had a significant increase in LDL cholesterol levels, whereas those in the placebo group had a significant reduction of this lipoprotein.[25]

Studies evaluating the effect of omega-3 fatty acids on SLE are listed in Table 1.

Table 1 – Interventional studies with omega-3 fatty acids in patients with systemic lupus erythematosus (SLE).

Study	n	Study design	Results
Clark *et al.*, 1989[17]	12 subjects with lupus nephritis	6 g of omega-3 supplements/day over five weeks, followed by five weeks with no supplements and additional five weeks with 18 g of omega-3/day	Rise in EPA and DHA levels in membrane phospholipids and decrease in AA levels Decreased platelet aggregation and blood viscosity Increased red-cell flexibility Reduced LTB4 production by neutrophils 38% reduction in triglyceride levels and 39% reduction of VLDL-C levels 28% increase in HDL-C levels No effects on anti-DNA and albuminuria levels
Westberg *et al.*, 1990[18]	60 subjects with moderately active SLE	Omega-3 supplements *vs.* placebo Supplements for six months	Improvement in clinical and laboratory parameters over the first three months with supplements Unchanged after six months with supplements
Clark *et al.*, 1993[19]	21 subjects with stable lupus nephritis	Supplements with 15 g of fish oil *vs.* olive oil placebo for one year	Unchanged kidney function and disease activity Reduced VLDL-C and triglyceride serum levels Unchanged LDL-C and HDL-C levels
Duffy *et al.*, 2004[20]	52 subjects with SLE	Four groups: (1) 3 g of omega-3 + 3 mg of copper; (2) 3 g of omega-3 + copper placebo; (3) 3 mg of copper + omega-3 placebo; (4) omega-3 and copper placebo Supplements for six months	Reduced disease activity in groups receiving omega-3
Nakamura *et al.*, 2005[21]	Six subjects with lupus nephritis	Supplements with daily doses of 1.8 g of purified EPA Supplements for three months	Reduced AA levels and increased EPA levels in membrane phospholipids Reduced urine levels of 8 isoprostane Unchanged anti-DNA and serum complement values
Wright *et al.*, 2008[22]	60 subjects with SLE	Supplements with 3 g/day of omega-3 *vs.* olive oil placebo Supplements for six months	Reduced disease activity Improvement of endothelial function Reduced oxidative stress
Aghdassi *et al.*, 2011[23]	32 subjects with SLE and 20 controls without the disease	Fatty acid contents in red cells and plasma from: women with and without SLE; between SLE patients with and without a history of CVD; between patients taking corticosteroids or not were compared	Lower omega-3 levels in red-cell membrane of subjects with SLE than in those without the disease Higher plasma omega-6 fatty-acid levels in patients with SLE and a history of CVD Higher omega-3 levels in patients taking corticosteroids Differences, however, were not statistically significant
Elkan *et al.*, 2012[24]	114 SLE patients and 122 subjects without the disease	Omega-3 and omega-6 contents in adipose tissue cells of patients with SLE were evaluated	Negative association between higher EPA and DHA levels in adipose tissue cells and disease activity and presence of atherosclerotic plaques Positive association between higher omega-6 levels in adipose tissue cells, damage index, and presence of atherosclerotic plaques
Bello *et al.*, 2013[25]	85 subjects with SLE	Supplements with 3 g of omega-3/day *vs.* placebo Supplements for 12 weeks	Unchanged endothelial function and disease activity Increased LDL-C levels in subjects receiving omega-3 Unchanged levels of inflammatory markers (IL-6, ICAM-1, and VCAM-1)

SLE, systemic lupus erythematosus; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; LT, leukotriene; VLDL-C, very-low-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; AA, arachidonic acid; CVD, cardiovascular disease; IL, interleukin; ICAM, intercellular adhesion molecule; VCAM, vascular adhesion molecule.

Final remarks

Clinical studies suggest that supplementation with omega-3 polyunsaturated fatty acids can represent an additional option to SLE standard pharmacological treatment because of their anti-inflammatory properties.[17–25] This lipid class is related to the production of eicosanoids with a lower inflammatory action than those produced by fatty acids pertaining to the omega-6 family, additionally reducing serum levels of inflammatory cytokines and T lymphocyte activation.

Clinical trials conducted used very different doses, ranging from 1.8 g to 18 g of fish oil, and different treatment lengths, ranging from five weeks to 12 months. Whether positive effects are caused by EPA intake, DHA intake or by a combined action of both fatty acids is questionable. In addition, most studies have small numbers of subjects included, therefore leading to limited conclusions.

Thus, further studies with a larger number of subjects are needed to evaluate the real effect of these fatty acids in patients with SLE, the effective dose, and the duration of treatment.

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Conflicts of interest

The authors declare no conflicts of interest.

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