Omega-3 long-chain polyunsaturated fatty acids supplementation on inflammatory biomarkers: a systematic review of randomised clinical trials

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Abstract

Inflammation is part of the normal host response to infection and injury. Eicosanoids, cytokines, chemokines, adhesion molecules and other inflammatory molecules are frequently produced during this process. Numerous studies in humans have documented the inflammation-limiting properties of omega-3 fatty acids, but only a few have been randomised clinical trials. The aim of this study was to perform a systematic search of randomised clinical trials on omega-3 fatty acids and inflammatory biomarkers in all subjects including healthy and ill persons up to February 2011 using PubMed and LILACS databases, defined by a specific equation using MeSH terms and limited to randomised clinical trials; there was no any a priori decision to include some diseases and not others. The quality of each publication was validated by using the JADAD scale and the CONSORT checklist. Inflammatory biomarkers were considered as primary outcomes. Twenty-six publications of the last 10 years were selected. Studies included healthy subjects and patients with cardiovascular disease and other chronic and acute diseases; all reported the number of subjects, type of study, type and doses of omega-3 fatty acids, main outcomes and major inflammatory biomarkers. Dietary omega-3 fatty acids are associated with plasma biomarker levels, reflecting lower levels of inflammation and endothelial activation in cardiovascular disease and other chronic and acute diseases, including chronic renal disease, sepsis and acute pancreatitis. However, further research is required before definitive recommendations can be made about the routine use of omega-3 fatty acids in critically ill patients or with neurodegenerative or chronic renal disease.

Key words: Acute Diseases; Biomarkers; Chronic Diseases; Cytokines; Eicosanoids; Inflammation; Omega-3 fatty acids; Systematic review; Inflammation

Introduction

Inflammation is an ordered sequelae of events engineered to maintain tissue and organ homeostasis. The timely release of mediators and expression of receptors is essential to complete the programme and restore tissues ad integrum. Inflammation is characterised by redness, swelling, heat, pain and numerous physiological changes, including increased blood flow and permeability across blood capillaries. These changes allow large molecules to leave the bloodstream and cross the endothelial wall, increasing the migration of leukocytes from the bloodstream into the surrounding tissue. Inflammation results from immunological processes in response to injury, invading pathogens, allergens and toxins and leads to repair of the damaged tissue. The first cells detected at inflamed sites are granulocytes, monocytes and macrophages, which have a role in killing pathogens and clearing cellular and tissue debris as well as in tissue repair; lymphocytes appear at a later stage.1–3

Inflammation can be classified into two types: a) acute inflammation, with a rapid course (from minutes to a few days), in which the most important events are oedema and the migration of leukocytes, mainly granulocytes and monocytes; and b) chronic inflammation, characterised by a long time course, the presence of lymphocytes and macrophages and the proliferation of blood vessels and connective tissue. Hence, an exaggerated inflammatory response can cause local tissue damage and remodelling, which may induce significant and chronic injury. Inflammation underlies and/or accompanies numerous prevalent diseases, including cardiovascular diseases, obesity, diabetes, cancer, inflammatory bowel diseases, neurodegenerative diseases, rheumatoid arthritis and asthma.4,5

The inflammatory response is regulated by a complex network of mediators. Active mediators modify tissues and organs and specifically adapt their response to each inflammatory inducer signal; these signals increase the production of inflammatory mediators.6

Chemical mediators of inflammation (CMFs) have been described as biomarkers of inflammation for both healthy individuals and patients with chronic disease.6,7 There are eight CMF groups: acute phase protein reactants (C-reactive protein [CRP]), vasoactive amines, vasoactive peptides, fragments of complement components (C3a, C4a, C5a), lipid mediators (eicosanoids, docosanoids and platelet-activating factors),

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cytokines, chemokines and proteolytic enzymes\(^9\). Reactive free radicals, particularly reactive oxygen species (ROS) are major mediators of various acute and chronic inflammatory conditions\(^9\).

Bacterial endotoxins can directly activate monocytes and macrophages, inducing them to form: cytokines, e.g., tumour necrosis factor (TNF-\(\alpha\)), interleukins (IL-1, IL-6, IL-8), chemokines, e.g., monocyte chemotactic protein 1 (MCP-1) and macrophage inflammatory protein 1 alpha (MIP-1\(\alpha\)); eicosanoids, e.g., PGE\(_2\) and LTB\(_4\); nitric oxide; matrix metalloproteinases (MMPs) and other mediators, which also regulate body response to infection and injury. In addition to eicosanoids, a number of long-chain polyunsaturated fatty acid (LC-PUFA) derivatives are involved in resolving the inflammatory process, notably lipoxins, resolvins and protectins, recently described as major biomarkers of inflammation\(^8,10,11\).

When TNF-\(\alpha\), IL-1 and IL-6 are present in high concentrations, they are especially destructive and implicated in pathological responses in endotoxic shock, in acute respiratory distress syndrome, and in chronic inflammatory diseases, e.g., rheumatoid arthritis and inflammatory bowel disease. Chronic overproduction of TNF-\(\alpha\) and IL-1 can damage adipose tissue and muscle and produce loss of bone mass. Anti-inflammatory cytokines (e.g., IL-10) and receptor antagonists (e.g., IL-1R) oppose the cascade of inflammatory mediators initiated by inflammatory cytokines\(^3\)–\(^12\).

In addition to CMFs, upregulation of adhesion molecules on the endothelial cell surface allows leukocyte binding and subsequent diapedesis and is a well-known step of inflammation in some chronic diseases, e.g., cardiovascular diseases; these molecules include intercellular adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1) and E-Selectin\(^(2,12–15)\).

The ability of dietary omega-3 LC-PUFA to limit inflammation has been demonstrated in numerous studies of animals and humans under different conditions and using varied doses. Its intake is associated with reduced concentrations of CRP, proinflammatory eicosanoids, cytokines, chemokines and other inflammation biomarkers\(^15\). However, only some of these studies were properly designed to provide evidence of the influence of dietary omega-3 intake on specific inflammatory biomarkers. The aim of the present review was to systematically review evidence on the effect of dietary omega-3 fatty acid (FA) supplementation on inflammatory biomarkers in healthy subjects and in patients with chronic and acute inflammatory diseases.

**Methods**

The research question in this systematic review was “Does omega-3 LC-PUFA affect biological levels of inflammatory biomarkers?” It included all randomised controlled trials (RCTs) in humans, both healthy and ill subjects, in which the effect of omega-3 LC-PUFA on fluid (mainly plasma or serum and cerebrospinal fluid) and cellular levels of inflammatory biomarkers was compared with that of placebo; inflammatory biomarkers were considered as primary outcomes. RCTs with prospective, parallel or crossover designs were all considered. The papers, or at least the abstract, had to be in English, but there was no restriction on publication type or sample size. We did not include any cohort, ecological or case-control study.

**Inclusion and exclusion criteria**

For a study to be considered, dietary supplementation or a specific diet had to be administered, excluding those on dietary recommendations or self-reporting alone. Studies were also excluded if a supplement was administered that could potentially lead to confounding the effects of omega-3 fatty acids (FA) and if there was no ethical approval. Particularly, five studies in which arginine and omega-3 FA were used together as supplement sources were excluded.

**Participants**

Eligible participants were individuals of all ages, either healthy or with acute or chronic disease. There was no restriction on the basis of gender, ethnicity, study setting or other characteristics.

**Types of intervention**

LC-PUFA treatments were selected, including eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA) or docosapentaenoic acid (DPA), either individually or in combination with each other or with another pharmacological treatment (or vitamin supplementation) if the study design allowed the effect of omega-3 FA to be isolated. There were no restrictions with regard to dosage or dose regimen.

**Primary outcome measures**

These had to include changes in the following inflammatory biomarkers: acute phase reactant proteins (PCR), eicosanoids (PGE\(_1\), PGE\(_2\), LTB\(_4\), \(F_2\)-isoprostanes), cytokines (IL-1\(\alpha\), IL-1\(\beta\), IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12p70, IL-13, TNF-\(\alpha\), interferon-\(\gamma\)), chemokines (CCL2, CCL3, CCL5, CCL11), adhesion molecules (sVCAM-1, sICAM-1, sE-selectin, sP-selectin) and related biofactors (sIL-1RII, sIL-6R, sTNF-Rs 1 and 2, CD11b, CD18, CD49, CCR2 and CCR5, MMP-7, MMP-9, MMP-12, TIMP-2, \(\alpha\)-1-nichymotrypsin, fibrinogen, PAI-1, orosomucoid AGP), comparing measurements between baseline and the end of the intervention. Studies that did not evaluate inflammatory biomarkers were excluded.

**Main stages of the systematic review**

The main stages in the classification of studies for this systematic review are depicted in Fig. 1. Studies were identified on the PubMed database on February 11, 2011, without restriction on publication date until the search date, using the following equation: #1 “Fatty Acids, Omega-3”[MeSH] AND “Inflammation”[MeSH], which yielded 365 different articles. Next, the equation was modified to: #2 “Fatty Acids, Omega-3”[MeSH] AND “Inflammation”[MeSH] AND “humans”[MeSH Terms],

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yielding 172 results. A more specific search was then conducted for RCTs, using: “Fatty Acids, Omega-3” [MeSH] AND “Inflammation” [MeSH] AND “humans” [MeSH Terms] NOT “Review” [All Fields] AND “Randomised Controlled Trial” [ptyp]. This search generated 58 original articles, out of which 26 met all requirements for inclusion in the review. The LILACS database was also searched on February 11 2011 but yielded no results.

A tool, known as SYSCOLLAB (see Chapter 1), was developed and used for the selection, classification and validation of these articles, following the procedures described below.

**Study Selection.** Abstracts of references obtained by the search were examined by four reviewers (AG, CMA, MDM, ODR), who eliminated all references evidently ineligible for inclusion. Each reviewer studied all of the remaining full texts independently and made a selection. In cases of disagreement, a consensus was reached on the final list after discussion among all four reviewers.

**Data extraction.** Two reviewers (AG, ODR) introduced the data into a database, and discrepancies between them were resolved by a third reviewer (CMA). Missing data were obtained from the authors whenever possible, solicited on specific forms to avoid bias.

**Assessment of quality.** The quality of each publication was validated by applying the JADAD scale and the CONSORT checklist for clinical trials. JADAD establishes the quality level according to five items and the use of the CONSORT checklist ensures that publications follow quality guidelines. We developed a quantitative scale by assigning a value to each item in the list, as shown in Table 1, giving a quality score ranging from 0 to 30 (low to excellent).

**Results**

Table 2 lists the 26 publications selected for inclusion in the review, grouped according to study population (healthy, cardiovascular disease, other chronic diseases and acute disease). It also indicates the sample size, type of study, type and dose of omega-3 FA administered, major inflammatory biomarkers determined and main outcomes.

**Healthy individuals**

Out of the 26 selected articles, 10 reported data on the effect of dietary omega-3 FA on inflammatory biomarkers in healthy participants. Quality scores for these studies ranged from 3 to 5 for the JADAD scale, and from good to excellent (G-E) for the CONSORT scale. All 10 studies were in healthy adults (sample sizes from 12 to 161): three in young adults (19–40 years), six in the middle-aged (40–65 years) and one in the elderly (>65 years). Two of these studies investigated the effects of omega-3 dietary supplementation on exercise-induced markers of inflammatory mediators in exercise-trained men (Table 2). In eight of these studies, omega-3 was delivered in fish oil capsules at daily doses of 0.12–2.22 g of EPA and 0.26–0.56 g of DHA, alone or in combination, for 2–26 weeks. One study supplied 0.6 g EPA and 0.2 g DHA daily in supplemented soybean milk for 12 weeks, while another provided 2 ml/day of fish oil (87 mg EPA and 72 mg DHA) and 2 ml/day of fish oil (87 mg EPA and 50 mg DHA), administered using a dropper. Only one study investigated the effect of parenteral lipid infusion (+55–9.8 g EPA +4.9–10.9 g DHA), for a period of 48 h and with cross-over repetition of the infusion after 3 months.

Inflammation outcome variables in the above studies were serum markers, including CRP, cytokines (IL-1α, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12p70, IL-13, TNF-α, interferon-γ), chemokines (CCL2, CCL3, CCL5, CCL11) and soluble forms of cell adhesion molecules (ICAM-1, VCAM-1, E-Selectin). Four of the studies investigated the effects of omega-3 supplementation on peripheral blood cell levels of inflammatory markers induced by lipopolysaccharides (LPS) or endotoxins, including eicosanoids (PGE1, PGE2, LTB4) and cytokines (IL1 β, IL 6, IL 8, IL10 and TNF-α). Only one study measured the expression of adhesion molecules in monocytes (CD11b, CD18, CD49, CCR2 and CCR5).

Five studies determined the effect of omega-3 supplementation on serum CRP levels in healthy individuals, with one report detecting no effect in healthy volunteers without active inflammation, whereas another found lower exercise-induced serum CRP levels after EPA/DHA supplementation in trained men.

Omega-3 supplementation did not significantly affect the serum concentration of any of the cytokines and chemokines analysed in healthy individuals, with the exception of a reduction in exercise-induced TNF-α.

Plasma soluble forms of cell adhesion molecules were measured in three of these studies, finding no effects except for a decrease in sICAM-1 and sVCAM-1 after supplementation with 1.8 g EPA plus 0.3 g DHA (8 weeks).
Table 2. Characteristics of selected studies (18–40)

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<tr>
<th>Author and Country</th>
<th>CONSORT Score</th>
<th>Participants/Type of Pathology/Age</th>
<th>RCT Type</th>
<th>Dose/Period</th>
<th>Outcome</th>
<th>Conclusions</th>
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<tbody>
<tr>
<td>Healthy subjects Pot et al. (2009) Netherlands</td>
<td>VG</td>
<td>n 77; (Exptal = 39; Placebo = 38); Healthy middle-aged adults (50–70 years),</td>
<td>Randomised, double-blinded, placebo-controlled.</td>
<td>3·5 g/day fish oil (1·5 g/day total n-3 PUFA); 12 weeks</td>
<td>IL-1α, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12p70, IL-13, TNF-α, Interferon-γ, CCL2, ICAM-1, VCAM-1, CCL3, CCL5, CCL11</td>
<td>1·5 g/day n-3 PUFA did not affect serum inflammatory biomarkers.</td>
</tr>
<tr>
<td>Bouwens et al. (2009) Netherlands</td>
<td>VG</td>
<td>n 111; (High EPA = 36; Low EPA = 100; HOSF = 106); Healthy adults (&gt; 65 years)</td>
<td>Randomised, placebo-controlled</td>
<td>High-dose: 1·8 g EPA + DHA; Low-dose: 0·4 g DHA + EPA; HOSF; 26 weeks</td>
<td>Inflammatory gene expression.</td>
<td>Intake of EPA + DHA for 26 weeks can change the gene expression profile of PBMCs to a more anti-inflammatory and anti-atherogenic status.</td>
</tr>
<tr>
<td>Yusof et al. (2008) UK</td>
<td>VG</td>
<td>n 21; (Exptal = 10; Placebo = 11); Healthy middle-aged men (43·7 ± 2·3 years; 44·7 ± 2·0 years)</td>
<td>Randomised, double-blinded, placebo-controlled.</td>
<td>EPA = 1·8 g/d + DHA = 0·3 g/d; 8 weeks</td>
<td>IL-6, s-E-Selectin, sICAM-1, sVCAM-1, CRP, sP-Selectin.</td>
<td>Marine oil providing 1·8 g EPA plus 0·3 g DHA/day is not sufficient to demonstrate marked anti-inflammatory effects, as indicated by the decrease in sICAM-1.</td>
</tr>
<tr>
<td>Schubert et al. (2007) Germany</td>
<td>G</td>
<td>n 30; (Exptal = 15; Placebo = 15); Healthy adults (27·8 ± 1·2 years; 27·8 ± 1·0 years)</td>
<td>Randomised, double-blinded, placebo-controlled.</td>
<td>3 capsules (total: 0·24 g/d ALA, 0·12 g/d EPA, 0·49 g/d STA and 0·73 g/d GLA); 2 weeks</td>
<td>IL-8, IL-10, TNF-α, PGE1, PGE2, LTβ2.</td>
<td>No significant effects on inflammatory biomarkers.</td>
</tr>
<tr>
<td>Fujioka et al. (2006) Japan</td>
<td>G</td>
<td>n 161; (Exptal = 81; Placebo = 76); Healthy middle-aged adults (38·8 ± 11·6 years; 37·0 ± 11·5 years)</td>
<td>Randomised, double-blinded, placebo-controlled.</td>
<td>EPA = 0·60 g/d + DHA = 0·26 g/d; 12 weeks</td>
<td>hsCRP, sTNF-Rs 1 and 2.</td>
<td>Fish oils do not change inflammatory parameters such as hs-CRP and sTNF-Rs 1 and 2 in subjects without active inflammation.</td>
</tr>
<tr>
<td>Murphy et al. (2006) Australia</td>
<td>G</td>
<td>n 50; (Exptal = 12; Control = 13); Healthy adults (43 ± 10 years; 39 ± 9·5 years)</td>
<td>Randomised, double-blinded, parallel.</td>
<td>2 ml NZOML oil (EPA = 0·087 g/d and DHA = 0·072 g/d) and 2 ml fish oil (EPA = 0·087 g/d and DHA = 0·05 g/d); 6 weeks</td>
<td>PGE2, IL-1β and TNF-α.</td>
<td>Low dose supplementation with n-3 LC-PUFA from two different marine oil preparations showed no difference in inflammatory markers in this group of healthy individuals. A fish oil-based omega-3 lipid emulsion significantly suppresses monocyte proinflammatory cytokine generation and features of monocyte recruitment.</td>
</tr>
<tr>
<td>Mayer et al. (2003) Germany</td>
<td>G</td>
<td>n 12; Healthy adults (&gt; 18 years)</td>
<td>Randomised, double-blinded, crossover design.</td>
<td>EPA = 4·55 - 9·8 g/d + DHA = 4·9 - 10·9 g/d; 2 periods of 48 hours (See note 1)</td>
<td>CD11b, CD18, CD49, CCR2 and CCR5</td>
<td>A moderate increase in consumption of long-chain n-6 or n-3 PUFA does not significantly affect inflammatory cell numbers or neutrophil and monocyte responses in humans and would not be expected to cause immune impairment.</td>
</tr>
<tr>
<td>Thies et al. (2001) UK</td>
<td>G</td>
<td>n 48; (8 groups; n 8 each one); Healthy adults; (55–74 years)</td>
<td>Randomised, double-blinded, placebo-controlled.</td>
<td>9 capsules/day(EPA = 0·72 g/d + DHA = 0·28 g/d); 12 weeks</td>
<td>Leukocytes, TNF-α, IL-1β, IL-6, sICAM-1, sVCAM-1, sE-Selectin.</td>
<td>A moderate increase in consumption of long-chain n-6 or n-3 PUFA does not significantly affect inflammatory cell numbers or neutrophil and monocyte responses in humans and would not be expected to cause immune impairment.</td>
</tr>
<tr>
<td>Nieman et al. (2009) USA</td>
<td>G</td>
<td>n 23; (Exptal = 11; Placebo = 12); Healthy endurance athletes (24·1 ± 2·4 years; 24·9 ± 2·8 years)</td>
<td>Randomised, double-blinded, placebo-controlled</td>
<td>4 capsules (EPA = 2 g/d + DHA 0·4 g/d); 6 weeks</td>
<td>CRP, Creatine kinase, IL-1, IL-6, IL-8.</td>
<td>2·4 g/d EPA and DHA supplementation for 6 weeks by trained cyclists did not improve 10-km time-trial performance or alter inflammation or immunity before or after 3 days of prolonged and intensive exercise when compared with placebo. EPA/DHA supplementation increases blood levels of these fatty acids and results in decreased resting levels of inflammatory biomarkers in exercise-trained men, but it does not appear necessary for exercise-induced attenuation in either inflammation or oxidative stress.</td>
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## Table 2. Continued

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<tr>
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<tbody>
<tr>
<td>Cardiovascular diseases</td>
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<tr>
<td>Cawood et al. (2010) UK, Norway</td>
<td>VG</td>
<td>n 121; (Exptal = 60; Control = 61); Carotid endarterectomy (&gt; 18 years)</td>
<td>Randomised, double-blinded, placebo-controlled.</td>
<td>EPA = 0.81 g/d + DHA = 0.675 g/d; median of 21 days</td>
<td>Macrophage and T lymphocytes in Carotid Plaque, mRNA of MMP-7, MMP-9, MMP-12, IL-6, ICAM-1, TIMP-2</td>
<td>Advanced atherosclerotic plaques appear to readily incorporate EPA from n-PUFA ethyl esters, and a higher content of EPA in carotid plaques is associated with a reduced number of foam cells and T cells, less inflammation and increased stability</td>
</tr>
<tr>
<td>Zhao et al. (2009) China</td>
<td>VG</td>
<td>n 76; (Exptal = 38; Placebo = 38); Heart failure; (&gt; 60 years)</td>
<td>Prospective, single-blind, randomised, placebo controlled.</td>
<td>2 g n-3 PUFA (EPA = 0.18 g + DHA = 0.12 g) as ethyl esters per gram/day; 3 months</td>
<td>hsCRP, TNF-α, IL-6, ICAM-1, VCAM-1</td>
<td>n-3 PUFA can decrease plasma levels of the pro-inflammatory cytokines IL-6, TNF-α and ICAM-1 in patients with chronic heart failure and can reduce plasma NT-proBNP concentrations as biomarkers of risk stratification in heart failure.</td>
</tr>
<tr>
<td>Nilsen et al. (1993) Norway</td>
<td>G</td>
<td>n 20; (Exptal = 10; Placebo = 10) Coronary heart disease (NA)</td>
<td>Randomised, double-blinded, placebo-controlled.</td>
<td>Concentrated ethyl ester 6 g/d; 2 months</td>
<td>PAI-1</td>
<td></td>
</tr>
<tr>
<td>Tulk and Robinson (2008) Canada</td>
<td>G</td>
<td>n 8; Metabolic syndrome; (&lt; 45 years)</td>
<td>Randomised, crossover design</td>
<td>Modification of n-6/n-3 ratio in a high-saturated fatty acid oral fat tolerance test; 3 trial days</td>
<td>CRP, IL-6, sIL-6R.</td>
<td></td>
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<tr>
<td>Browning et al. (2007) UK</td>
<td>VG</td>
<td>n 33; (Exptal = 15; control, 18); Overweight women with inflammatory phenotype (NA)</td>
<td>Randomised crossover design.</td>
<td>1 g capsule/day (EPA = 1.3 g/d + DHA = 2.9 g/d); 12 weeks</td>
<td>α1-antichymotrypsin, fibrinogen, PAI-1, orosomucoid AGP, CRP, IL-6.</td>
<td>Habitual inflammatory status influences the impact of n-3 LC-PUFA supplementation, but it is not clear whether the effect of these PUFA on AUC insulin is mediated through inflammatory mechanisms.</td>
</tr>
<tr>
<td>Engler et al. (2005) USA</td>
<td>VG</td>
<td>n 20; Hyperlipidaemic children (9–19 years)</td>
<td>Randomised, double-blinded, placebo controlled crossover design.</td>
<td>DHA = 1.2 g/d; 6 weeks.</td>
<td>CRP</td>
<td></td>
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<tr>
<td>Mori et al. (2003) Australia</td>
<td>G</td>
<td>n 59; (Exptal EPA = 17; Exptal DHA = 17; Placebo = 16); Type 2 Diabetes (40–75 years)</td>
<td>Double blind, placebo controlled, parallel design.</td>
<td>4 g/d of EPA (96 %) + DHA (92 %); 6 weeks</td>
<td>CRP, TNF-α, IL-6</td>
<td></td>
</tr>
<tr>
<td>Skulas-Ray et al. (2011) USA</td>
<td>E</td>
<td>n 28; Hypertriglyceridemia (21–65 years)</td>
<td>Randomised, double blind, placebo-controlled, 3-period crossover design.</td>
<td>EPA = 0.85 g/d and DHA = 3.4 g/d; 8 weeks</td>
<td>CRP, TNF-α, IL-6, IL-1β</td>
<td>The 3.4 g/d dose of EPA + DHA significantly lowered triglycerides, but neither dose improved endothelial function or inflammatory status over 8 weeks in healthy adults with moderate hypertriglyceridemia.</td>
</tr>
<tr>
<td>Other chronic diseases and critically ill patients</td>
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<tr>
<td>Bowden et al. (2009) Netherlands</td>
<td>E</td>
<td>n 33; (Exptal = 18; Control = 15) End-stage renal disease (57.2 ± 12.8 years, 64.3 ± 14.2 years)</td>
<td>Double-blind, permuted-randomised and placebo-controlled.</td>
<td>EPA = 0.96 g/d + DHA = 0.6 g/d; 6 months</td>
<td>CRP</td>
<td>Consuming 0.96 g/d of EPA and 0.6 g/d of DHA can lower CRP.</td>
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<tr>
<td>Perunicic-Peko-vic et al. (2007) Serbia and Montenegro</td>
<td>E n 42; (Exptal = 26; Control = 16) Chronic renal disease (55 ± 8 years)</td>
<td>RCT Type</td>
<td>2-4 g/d n-3 PUFA; 2 months</td>
<td>IL-6, TNF-α</td>
<td>A dietary regimen with fish oil could be used in dialysis patients to slow down the development of atherosclerosis and improve nutritional parameters.</td>
<td></td>
</tr>
<tr>
<td>Freund-Levi et al. (2009) Sweden</td>
<td>G n 38; (Exptal = 18; Placebo = 20) Alzheimer’s Disease (72-2 ± 8-8 years, 68-3 ± 7-3 years)</td>
<td>Randomised, double-blinded, placebo-controlled.</td>
<td>EPA = 0-15 g/d + DHA = 0-43 g/d; 6 months</td>
<td>IL-6, TNR-α, sIL-1RII, CRP, APOE genotype (possible relationship)</td>
<td>Treatment of AD patients with omega-3 FA for 6 months did not influence inflammatory biomarkers in CSF or plasma.</td>
<td></td>
</tr>
<tr>
<td>Vedin et al. (2008) Sweden</td>
<td>E n 25; (Exptal = 9; Placebo = 12) Alzheimer’s disease (73 ± 9 years)</td>
<td>Randomised, double-blinded, placebo-controlled.</td>
<td>EPA = 0-6 g/d + DHA1-7 g/d; 6 months</td>
<td>IL-6, IL-1β, TNF-α, IL-2, IL-4, IL-5, IL-8, IL-10, Interferon-?</td>
<td>AD patients treated with DHA-rich n-3 FA supplementation increased plasma concentrations of DHA and EPA, which were associated with reduced release of IL-1β, IL-6 and granulocyte colony-stimulating factor from PBMC’s.</td>
<td></td>
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<tr>
<td>Barbosa et al. (2010) UK</td>
<td>E n 23; (Exptal = 10; Control = 13) Sepsis (32–80 years)</td>
<td>Randomised, single-blinded.</td>
<td>6-4 g/d fish oil (Average 1-6 g EPA/day + 0-7 g DHA/ day); 5 days</td>
<td>PGE2, Leukotriene, IL-1β, IL-6, IL-10 and TNF-α</td>
<td>Inclusion of fish oil in parenteral nutrition of septic ICU patients increases plasma EPA, modifies inflammatory cytokine concentration and improves gas exchange.</td>
<td></td>
</tr>
<tr>
<td>Mayer et al. (2003) Germany</td>
<td>VG n 10; (Exptal = 5; Control = 5) Sepsis shock (31–71 years)</td>
<td>Randomised, open label.</td>
<td>EPA = 5-2-11-2 g + DHA = 5-6–12-4 g; 10 days (See note 2)</td>
<td>CRP, Leukocytes.</td>
<td>Omega-3 and omega-6 lipid emulsions differentially influence the plasma free fatty acid profile with impact on neutrophil functions.</td>
<td></td>
</tr>
<tr>
<td>Mayer et al. (2003) Germany</td>
<td>VG n 21; (Exptal = Control = 6) Sepsis (&gt; 18 years)</td>
<td>Randomised, open label.</td>
<td>EPA = 4-55–9-8 g/d + DHA = 4-9–10-9 g/d; 5 days (See note 3)</td>
<td>IL-1β, IL-6, IL-8, IL-10, TNF-α</td>
<td>Use of lipid infusions and intravenous feeding have differential impact on inflammatory events.</td>
<td></td>
</tr>
<tr>
<td>Wang et al. (2008) China</td>
<td>E n 40; (Exptal = 20; Placebo = 20) Severe acute Pancreatitis (18–80 years)</td>
<td>Randomised, double-blinded and placebo controlled.</td>
<td>0-15–0-2 g/kg/d fish oil (10 % Omegaven); 5 days</td>
<td>CRP</td>
<td>PN supplemented with omega-3 FA diminishes the hyperinflammatory response in severe acute pancreatitis.</td>
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</table>

and 0.72g EPA plus 0.28g DHA (12 weeks), respectively. This fish oil supplementation significantly decreased the release of PGE$_1$, and LT$_B$, alone after ex vivo LPS stimulation$^{21}$, whereas parenteral omega-3 lipid emulsion significantly suppressed the generation of TNF-$\alpha$, IL-1, IL-6 and IL-8 by monocytes in response to LPS, although their surface expression of relevant adhesion molecules was unchanged$^{29}$. Finally, only the study by Bouwens et al.$^{20}$ examined the effect of omega-3 intake on gene expression in peripheral blood mononuclear cells (PBMCs), finding that EPA + DHA intake reduced the expression of genes involved in inflammatory-related pathways, such as nuclear transcription factor kB (NF- kB) signaling and eicosanoid synthesis.

Cardiovascular disease

Eight of the articles selected in this review addressed the effect of omega-3 LC-PUFA on inflammatory molecules as biomarkers of CVD risk$^{27–33,41}$, with quality scores ranging from 3 to 5 for the JADAD scale and from good to excellent (G-E) for the CONSORT scale. Seven of these studies were in adults (>18 years) and only one was in hyperlipidaemic children and young people (9–19 years)$^{31}$. The study populations in the eight selected studies comprised: chronic heart failure patients with presence or high risk of CVD$^{28}$; patients awaiting carotid endarterectomy$^{27}$; patients undergoing coronary bypass surgery$^{41}$; patients with metabolic syndrome$^{29}$ or type 2 diabetes$^{32}$; overweight individuals$^{30}$; and people with moderate hyperlipidaemia but otherwise healthy$^{33}$.

All studies in this section used capsules to supply EPA and DHA, alone or combined, except for a postprandial study that administered an oily supplement (1g fat per kg body weight) containing 2.25% EPA plus 0.98% DHA in a high omega-3 PUFA blend or 0.37 EPA plus 0.16 DHA in a low omega-3 PUFA blend$^{29}$. When combined, EPA and DHA doses ranged from 0.6–3.6g EPA plus 0.24–4g DHA$^{28–30}$ to 6g/d$^{31}$ for 12 weeks. When administered alone, the regimen was 3.68g/d DHA for 13 or 6 weeks and 3.84g/d EPA for 6 weeks$^{32}$.

Outcome variables in the studies in this group were cytokines (IL-1B, IL-2, IL-6 and IL-6 soluble receptor, IL-8, IL-10, TNF-$\alpha$, TNF-R1, TNF-R2); serum markers, including CRP, $\alpha$1-antichymotrypsin (ACT), fibrinogen, tissue factor pathway inhibitor (PTPI), tissue plasminogen activator inhibitor (P-PAI-1), thrombin-antithrombin III (TAT) complexes, $\alpha$1-acid glycoprotein (AGP) and sialic acid; MMP2, soluble adhesion molecules (ICAM-1, VCAM-1, E-Selectin), pro-brain natriuretic peptide (NTproBNP), serum amyloid A (SAA), granulocyte colony stimulating factor (G-CSF) and granulocyte monocyte-colony stimulating factor (GM-CSF). There were also assessments of the expression of genes involved in inflammatory-related pathways, such as nuclear transcription factor kB (NF- kB) signaling and eicosanoid synthesis.

Cardiovascular disease

Evaluations of inflammatory markers were studied in chronic renal disease patients undergoing haemodialysis in two of the selected articles$^{34,35}$ and in patients with Alzheimer’s disease (AD) in another two$^{36,37}$. The quality scores for these articles ranged from 3 to 5 for the JADAD scale and from very good to excellent (V-E) for the CONSORT scale.

In the Bowden et al. study$^{34}$, eligible patients undergoing chronic haemodialysis maintenance were randomly assigned to an omega-3 (experimental, n 18) or corn oil (control, n 15) group. The experimental group received 960mg EPA/d plus 600mg DHA/d orally for 6 months, which had a significant effect on CRP levels not observed in the placebo group. Perunicic-Petric et al.$^{35}$ examined 42 haemodialysis patients and 16 healthy controls, administering the patients with daily supplements of 2.4g omega-3 LC-PUFA (180mg EPA and 120mg DHA) for 2 months, and reported a significant decrease in inflammatory markers (IL-6 and TNF-$\alpha$) in the supplemented group.

Vedin et al.$^{37}$ carried out an RCT in 174 AD patients who received 1.7g DHA plus 0.6g EPA or placebo for 6 months. The omega-3 group showed significant decreases in IL-6, IL-1 and G-CSF secretion after LPS stimulation of PBMCs. In addition, increases in the concentrations of DHA and EPA were negatively associated with IL-1 and IL-6 release in all of the patients. However, no decrease in the secretion of TNF-$\alpha$, IL-8, IL-10, or GM-CSF was observed. Freund-Levy et al.$^{36}$ found that omega-3 FA treatment for 6 months did not influence inflammatory biomarkers in cerebrospinal fluid (CSF) or plasma of patients with mild to moderate AD. In their study, 35 patients were randomly assigned to a daily intake of 2.3g omega-3 FA or placebo for 6 months, analysing CSF and plasma levels of IL-6, TNF-$\alpha$ and soluble IL-1 receptor type II at baseline and 6 months.

Other chronic diseases

Effects of omega-3 FA on inflammatory markers were studied in chronic renal disease patients undergoing haemodialysis in two of the selected articles$^{34,35}$ and in patients with Alzheimer’s disease (AD) in another two$^{36,37}$. The quality scores for these articles ranged from 3 to 5 for the JADAD scale and from very good to excellent (V-E) for the CONSORT scale.

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Acute diseases

Three of the selected articles studied the effects of omega-3 FA on inflammatory biomarkers in septic patients$^{23,58–60}$ and one investigated them in patients with severe acute pancreatitis$^{40}$.
Their quality scores ranged from 3 to 5 for the JADAD scale and from very good to excellent (V-E) for the CONSORT scales, respectively.

The studies in septic patients were randomised but single blind or open label. The treatment was short (5–7 days) in all three studies, and the omega-3 LC-PUFA dose ranged from 6–4 to 23 g/d. In the study by Barbosa et al., parenteral administration of fish oil emulsion significantly decreased IL-6 levels, with a parallel increase in IL-10, and improved the gas exchange, finding a tendency to a shorter hospital stay in patients receiving this supplementation.

Mayer et al. studied 21 patients with sepsis requiring parenteral nutrition, who were randomised to receive an omega-3 lipid emulsion rich in EPA and DHA or a conventional omega-6 lipid emulsion for 5 days. Generation of proinflammatory cytokines by mononuclear leukocytes was markedly amplified by omega-6 lipid intake and suppressed by omega-3 intake. Mayer et al. also studied ten patients with septic shock and eight healthy controls. Patients requiring Parenteral Nutrition (PN) received intravenously an omega-3 or omega-6 lipid emulsion (five per group) for a 10-day period. With the omega-6 lipid infusion regimen, the impairment of neutrophil functions persisted or worsened, whereas LTβr and LTβr appeared upon neutrophil stimulation in the omega-3 lipid group and neutrophil function was significantly improved.

Wang et al. performed an RCT in 47 severe acute pancreatitis patients randomly assigned to receive PN for 5 days with identical amounts of amino acids, glucose and fat but different lipid compositions. The control group received a soybean oil based emulsion and the omega-3 FA group was supplemented with 0.15–0.2 g/kg/d fish oil. Fish oil-treated patients had significantly lower CRP levels and blood cell counts after 5 days of PN.

Discussion

Omega-3 FA supplementation is known to lower inflammation biomarkers in the plasma and cells of patients with acute and chronic diseases, but its effect on healthy subjects is less well documented. Numerous authors have studied the combined effects of EPA and DHA but only a few have administered EPA or DHA alone. In addition, very few studies have investigated the effects of these FA on in vivo cell inflammatory biomarkers, on ex vivo cytokine release or on the expression of genes related to inflammation cascade signalling.

Healthy subjects

In the studies of healthy participants selected in this review, omega-3 supplementation generally had no effect on inflammatory biomarkers, which may be due to their low levels in serum, minimizing the possibility of their reduction through the intake of fish oil.

Fish oil supplementation was found to have only isolated effects on plasma soluble forms of cell adhesion molecules, reducing sICAM-1 and sVCAM-1 levels. The stronger association of DHA changes than EPA changes with sICAM described by Yusof et al. suggested that DHA may be more anti-inflammatory than EPA. However, this hypothesis was ruled out by the neutral effect on sICAM found by Thies et al., who used a very similar dosage of DHA (0.28 g vs. 0.3 g) alone or in combination with 0.72 g EPA during a longer period (12 vs. 8 weeks) and only found an influence on sVCAM-1 levels. The different effects of omega-3 on sICAM-1 and sVCAM-1 concentrations may suggest that VCAM-1 and ICAM-1 are regulated by different mechanisms and are not equally sensitive to n-3 PUFAs.

The release of cytokines after ex vivo LPS stimulation was not affected by oral administration of omega-3, but single blind or open label. However, in a study of healthy volunteers with a cross-over design, a decrease in LPS after parenteral administration of omega-3 lipid emulsion induced the production of cytokines (TNF-α, IL-1, IL-6 and IL-8), demonstrating that a short (48 h) infusion with omega-3 lipids is sufficient to significantly suppress monocyte proinflammatory cytokine generation. PN studies in healthy volunteers are rare and ethically questionable, making it impossible to draw conclusions about the anti-inflammatory effect of omega-3 in this situation.

Findings of the pioneering study by Bouwens et al. opened up a new approach for research into the effects of omega-3, demonstrating the potential of PBMC gene expression profiling for determining the effects of nutrition on human health status. However, this study was performed in elderly individuals, who are likely to express a slightly more proinflammatory gene expression profile, given that aging is associated with a chronic, low-grade elevation of inflammatory activity. Therefore, the results cannot be generalised to the whole population, and further research is required to confirm these findings in other age groups.

One way to investigate the effect of omega-3 supplementation on inflammatory markers in healthy individuals is to stimulate the inflammatory response by exercise. Transient inflammation and immune dysfunction are part of the normal human response to prolonged and intense exercise and are characterised in part by the production of inflammatory cytokines, acute-phase proteins and oxidative stress from reactive oxygen species, as well as by alterations in innate and adaptive immunity. However, conflicting results were published by two studies of inflammation. One found decreased levels of exercise-induced CRP, TNF-α and IL-6 after omega-3 supplementation, whereas the other observed no change in these levels. Discrepancies may be due to differences in the training status of participants, the duration of supplementation, the dose and FA composition of the n-3 PUFA administered, and the exercise protocol used. Thus, the two aforementioned studies differed in the total daily dosage of DHA (2208 mg vs. 400 mg) and exercise protocol (3 h/d cycling for 3 days vs. treadmill walking with weighted backpack for 60 min). The omega-3 supplementation was unable to counteract the acute inflammatory response induced in the former study, while it had no effect on the very weak inflammatory response induced by exercise in the latter, with the exception of decreased CRP and TNF-α levels at rest. In conclusion, the exercise-related omega-3-supplementation studies included in this review do not provide...
strong evidence of anti-inflammatory effects in trained or untrained participants.

**Cardiovascular diseases**

Results of selected articles on the effect of omega-3 LC-PUFA on inflammatory molecules as biomarkers of CVD risk remain inconclusive, and further studies are required. The evidence of clinical efficacy is not strong enough to make final recommendations for a specific dose or duration of supplementation.

The only inflammatory biomarkers affected by omega-3 PUFA in multiple studies were IL-6 and CRP, while TNF-α, sICAM-1 and GM-CSF were decreased in single studies. No effects on plasma biomarkers were found when omega-3 PUFA was administered for less than 12 wks, even at high doses, as shown by Nilsen et al. and Mori et al. However, shorter treatments may possibly induce changes in the mRNA expression of selected inflammatory genes by specific cells without affecting plasma levels, as observed by Caswood et al.

There is no consensus on the doses required to exert an anti-inflammatory effect, given that limited positive effects have been observed after low or high doses. It is therefore not possible to identify the dose needed to obtain an anti-inflammatory effect in patients with CVD risk.

In relation to the type of FA, most studies administered a combination of EPA plus DHA, and only Mori et al. compared the effects of EPA versus DHA supplementation (for 6 wks), reporting that neither had a significant effect. Hence, there is inadequate evidence to establish whether cardiovascular inflammation can be reduced by EPA or DHA or by the synergic effects of both.

Two of the studies showing an impact on IL-6 after omega-3 supplementation were reported to have inadequate power to detect a significant effect on inflammatory status, due to their small sample sizes (n 32, Browning et al., 2006, and n 38, Zhao et al., 2009). The same limitations apply to the effects on CRP, whose reduction was reported in the same studies. Specifically, Zhao et al. found omega-3 LC-PUFA to be associated with a decrease in plasma CRP levels in smokers but not in non-smokers. Although there is no consensus on the reproducible effects of cigarette smoke, it appears evident that smoking can increase the inflammatory response, and the results obtained by Zhao et al. suggest that smokers, with an increased inflammatory status, may take greater advantage of the anti-inflammatory effects of omega-3 PUFA.

Finally, the postprandial inflammatory response after an oral fat tolerance test was not modified by increasing omega-3 PUFA content, indicating that omega-3 PUFA does not have an acute effect and must be incorporated into cell membranes before exerting an anti-inflammatory effect.

Based on the results related to CVD risk examined in this review, there is inadequate evidence to establish a relationship between the consumption of omega-3 LC-PUFA and beneficial inflammatory biomarker outcomes, probably due to discrepancies in protocols, doses and treatment times. Further research is necessary to standardize protocols and determine suitable doses and regimens.

**Other chronic diseases**

Only two RCTs studied inflammatory biomarkers in AD, with contradictory results. Omega-3 FA affected the release of cytokines from blood mononuclear leukocytes but did not influence inflammatory biomarkers in CSF, although the correlation between soluble IL-1 receptor II (sIL-1RII) and amyloid peptide Aβ1-42 may reflect reciprocal interactions between IL-1 and Aβ peptides. However, it remains to be established whether omega-3 FA attenuate the release of cytokines from brain cells in AD.

CVD is a comorbid condition in patients with end-stage renal disease (ESRD) and is associated with a high mortality rate. The CVD risk in patients undergoing chronic haemodialysis can be ascribed to elevated serum lipid levels and blood pressure, although additional factors (e.g., acute phase reactants) may lead to a risk profile that is 10- to 20-fold higher in comparison to apparently healthy individuals and is responsible for the very high (50%) annual mortality in ESRD patients.

The use of omega-3 LC-PUFA has been proposed to control endothelial dysfunction and thereby control CRP levels. Additionally, ESRD patients do not usually consume enough omega-3 FA in their diet. The consumption of 960 mg/d of EPA and 600 mg/d of DHA can lower CRP in ESRD patients, even though there is no clinically significant change in their triglyceride levels. Furthermore, ESRD patients on haemodialysis who received 2.4 g of α-3 LC-PUFA per day for 2 months exhibited a significant decrease in inflammatory markers (IL-6 and TNF-α). However, compliance was not assessed. Further studies in ESRD patients are required to identify a complete set of biomarkers involved in inflammation.

**Acute diseases (Critically ill patients)**

In the cascade of inflammatory response during the acute phase of severe acute pancreatitis, PN supplemented with omega-3 FA is a treatment option for patients with systemic inflammatory response syndrome (SIRS) or sepsis complicated by multiple organ failure. After 5 days of PN plus omega-3 FA, severe acute pancreatitis patients had significantly lower CRP levels and blood white cell counts and showed improved respiratory function and shortened continuous renal replacement therapy time, suggesting that the systemic response to pancreatic and organ injury is attenuated by omega-3 LC-PUFA.

Omega-3 FA are thought to suppress inflammation and ameliorate the course of infection by reducing proinflammatory eicosanoids and cytokines. However, only one RCT assessed CRP changes, and further experimental studies and clinical trials are needed to establish the appropriate doses of omega-3 LC-PUFA and the specific effects of EPA and DHA on inflammatory biomarkers.

Novel potent lipid mediators derived from LC-PUFA, arachidonic acid (AA), EPA and DHA, namely lipoxins, resolvins, and protectins, have been identified in resolving exudates over recent years, and their biosynthetic pathways and actions
have been described. Their activity is likely to account in part for some of the immunoregulatory and disease-modifying actions attributed to dietary omega-3 LC-PUFA(49). However, no controlled studies in humans have evaluated the influence of omega-3 FA on these new lipid mediators.

Dietary recommendations of n-3 LC-PUFA in health and disease

A recent report of the FAO has established that for adult males and non-pregnant/non-lactating adult females 0.250 g/d of EPA plus DHA is recommended, with insufficient evidence to set a specific minimum intake of either EPA or DHA alone(50). The upper value of acceptable macronutrient distribution range for EPA+DHA consumption has been set at 2 g/d due to experimental evidence indicating that high supplement intakes of n-3 LC-PUFA may increase lipid peroxidation and reduce cytokine production. However, it is acknowledged that higher consumption values, as high as 3 g/d reduce some cardiovascular risk factors and have not had adverse effects in short- and intermediate term randomised trials.

The American Heart Association (AHA) recommended 0.5 to 1 g/d of omega-3 EPA and DHA for individuals with borderline fasting triglyceride levels (150 to 199 mg/dl), 1 to 2 g/d for individuals with high fasting-triglyceride levels (200–499 mg/dl), and 2 to 4 g/d for individuals with very high fasting-triglyceride levels (>500 mg/dl)(51).

Based in our study of RCT, a moderate consumption of n-3 LC-PUFA (0.9 to 2 g/d) does not change inflammatory biomarkers in healthy subjects(18–25). However, about 4 g/d of EPA/DHA supplementation decreases rest levels of inflammatory biomarkers in exercise-trained men, but it does not appear necessary for exercise-induced attenuation in either inflammation or oxidative stress(25). n-3 PUFA intake of 1-2 to 6 g/d decrease plasma levels of the pro-inflammatory cytokines and is associated with a reduced number of foam and T cells in atherosclerotic plaques(27) and with reduced levels of some inflammatory biomarkers in plasma(26). However, there is no consensus on the doses required to exert an anti-inflammatory effect(26–29). Regarding the effects of n-3 LC-PUFA on inflammatory biomarkers in neurodegenerative diseases, AD patients treated with DHA exhibit a reduced release of IL-1β, IL-6 and granulocyte colony-stimulating factor from PBMC(37). Furthermore, in patients with chronic renal disease, the intake of 1.5 to 2.4 g of n-3 LC-PUFA decreases CRP and other cytokines(53,54).

Omega-3 LC-PUFA are able to suppress inflammation and ameliorate the course of infection by reducing proinflammatory eicosanoids and cytokines in critically ill patients(43,48) but further research is needed before definitive recommendations can be made on doses and on the routine use of omega-3 FA in the critically ill.

Despite n-3 fatty acids reduce the risk of cardiovascular disease there has been concern that these fatty acids may increase lipid peroxidation. However, post-intervention urinary F2-isoprostanes were decreased by EPA and DHA in type 2 diabetic patients(32). In addition, it has been reported that supplementation with n-3 fatty acids decreases non-enzymatic free radical–catalyzed isoprostane formation in healthy humans(52). Likewise, plasma free F2-isoprostane concentrations were lower after fish-oil supplementation than after sunflower-oil supplementation in postmenopausal women(53). In conclusion, 3–4 g of n-3 LC-PUFA intake does not have an apparent effect on lipid peroxidation.

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Omega-3 fatty acids and inflammatory biomarkers


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