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Omega-3: Healthy Effects and Endpoints in Nutrition

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Abstract

The typically modern dietary imbalance among macronutrients leads to metabolic derangement of glucose and lipid disposal such as dyslipidemia, increased insulin resistance, and fatty liver, which are increasingly widespread all over the world and represent some of the characteristic features of the metabolic syndrome. Dietary fatty acids regulate several physiological functions, however, they have to be present in the diet in an optimal balance in order to exert their properties. Particular attention has been focused on n-3 polyunsaturated fatty acids and n-6/n-3 ratio, influenced by their dietary intake. Omega-3 fatty acids, which can be found both in terrestrial (especially in walnuts, flax, hemp and chia seeds) and in marine world (mostly in sardines, mackerel, salmon, halibut and krill) are essential for human functions, in particular for circulatory protection and, as a consequence, for the prevention of cardiovascular diseases. They result responsible for numerous cellular functions, such as signaling, cell membrane fluidity and structure maintenance. They also regulate nervous system, blood pressure, hematic clotting, glucose tolerance and inflammatory processes in general. Numerous studies are providing evidence about their use in order to prevent and treat several diseases. Cardiovascular diseases, lipid profile's alterations, mood disorders, asthma, cancer, and more in general all the inflammatory conditions can benefit from these valuable nutrients. For this reason, the daily intake of omega-3 fatty acids, properly balanced with omega-6, is crucial for any type of diet. Research has been carried out in animal models, tissue cultures, and humans: their beneficial effects have been shown in prevention and management of coronary heart disease, hypertension, type 2 diabetes, hepatic steatosis, rheumatoid arthritis, ulcerative colitis, Crohn's disease, mood disorders, dermatological pathologies and chronic obstructive pulmonary disease. Omega-3 resulted to be useful in all inflammatory conditions. This review highlights the importance of terrestrial and marine fatty acids in our diet, focusing on their role in contrasting inflammation and risk for development and progression of several diseases and illustrate the numerous fields of application of omega-3 in both prevention and treatment of chronic and inflammatory pathologies.

Keywords: Omega-3; Inflammation; Inflammatory Diseases; Seafood; Nutrition

Introduction

Omega-3 are polyunsaturated fatty acids (PUFAs) with more than one carbon-carbon double bound in their backbone, containing less than the maximum amount of hydrogen. They represent essential nutrients, resulting necessary for human health. We cannot synthesize omega-3 fatty acids, thus they have to be introduced through diet: they can be found not only in fish, such as sardines, salmon, tuna, halibut and other seafood, such as algae and krill [1], but also in lake trout, in some plants and nut oils. Omega-3 play a crucial role in brain function, physiological growth and development and may even reduce the risk of heart diseases. The American Heart Association recommends eating fatty fishes at least 2 times a week. Both omega-3 and omega-6 are stored in membrane phospholipids. These PUFAs are responsible for

numerous cellular functions: cell membrane structure, fluidity, signaling, and cell-to-cell interaction. Omega-3 fatty acids reduce inflammation and may help lower risk of chronic diseases such as heart disease, cancer, and arthritis. Symptoms of omega-3 fatty acid deficiency include fatigue, poor memory, dry skin, heart problems, mood swings or depression, and poor circulation. They also seem to regulate blood pressure, hematic clotting, glucose tolerance, and nervous system development and functions [2]. These compounds derived their name from the first double bound position, counting from the terminal carbon (carbon Omega, also indicated with "ω" or "n-"). The omega-3 are polyunsaturated because their chain comprises several double bonds. Among omega-3, there are: α-linolenic acid (18:3; ALA), eicosapentaenoic acid (20:5, EPA) and docosahexaenoic acid (22:6, DHA). Omega-3 fatty acids are also named "vitamin F" from "Fatty acids"[3]. Omega-3 fatty acids help reduce inflammation, and most omega-6 fatty acids tend to promote inflammation, so it is important to have the proper diet ratio of omega-3 and omega-6. The typical modern occidental diet tends to contain 14-25 times more omega-6 fatty acids than omega-3 fatty acids, which many physicians consider to be too high on the omega-6 side. The typical Mediterranean diet, on the other hand, which emphasizes foods rich in omega-3 fatty acids (Figure 1), has a healthier balance between omega-3 and omega-6 fatty acids. Many studies have shown that people who follow this diet are less likely to develop heart disease. Fish, plant, and nut oils are the primary dietary source of omega-3 fatty acids. Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are found in cold water fishes, which possess a greater quantity of body fat, although their content in EPA and DHA depends on some variables such as climate, environment and fish diet [4]. ALA is found in flaxseeds, canola (rapeseed) oil, soybeans, pumpkin seeds, purslane, perilla seed oil, walnuts and their derivative oils. Healthy effects come mostly from EPA and DHA. ALA from flax and other vegetarian sources needs to be converted in the body to EPA and DHA, unfortunately many people do not make these conversions very effectively. On the other side, fish oil is not suitable for vegetarians; in addition, the presence of chemical contaminants and heavy metals (firstly mercury and arsenic) in fish oil can be harmful to consumers [5,6]. Other important marine sources of omega-3 fatty acids include sea life such as krill, algae, microalgae and crustaceans. Krill oil, in particular Antarctic krill, is a rich source of both antioxidants, such as vitamins A-E and marine carotenoids (such as astaxanthin and fucoxanthin), and phospholipids containing long-chain omega-3 polyunsaturated fatty acids. In fact, alternative EPA and DHA marine sources such as sponges, bacteria, fungi, plants and, in particular, autotrophic macroalgae and microalgae, are currently being explored for large-scale commercial omega-3 production [7,8] because of their optimum balance between n-3 and n-6 fatty acids [9]. In particular, brown and red algae are characterized by the presence of EPA and ∝-linolenic acid [10]; green seaweeds, such as Ulva pertusa, are rich in hexadecatetraenoic acid [11]; octadecatetraenoic acid is found in Laminaria sp. and Undaria pinnatifida while hexadecatetraenoic acid is particularly abundant in Ulva sp. [12].

Figure 1. Main dietary sources of PUFAs

Seafood (85 grams)	EPA-DHA omega-3 (grams)	Terrestrial vegetables	ALA %
Flax	11.4	Flax/ linseed oil	59
Hemp	11.0	Chia seeds	58
Sardines	1.3–2	Hemp oil	19
Mackerel	1.1–1.7	Canola oil	11
Salmon	1.1–1.9	Butternuts	8.7
Halibut	0.60–1.12	Walnuts	6.3

Common Ground in Human Diseases: inflammation and role of Omega-3

Numerous experimental studies showed that dietary intake of n-3 fatty acids and the improvement in omega-6 and omega-3 ratio can modulate the immune and inflammatory response. After a supplementation with n-3 fatty acids (3.2 g EPA and 2.2 g DHA) an increased content of EPA in neutrophils and monocytes has been reported. The anti-inflammatory effects of fish oils are partly mediated by inhibiting the 5-lipoxygenase pathway in neutrophils and monocytes and inhibiting the leukotriene B4 (LTB4)-mediated function of leukotriene B5 (LTB5). In addition, n-3 fatty acids act on metabolism by decreasing interleukin IL-1 and IL-6. Inflammation is a common base for most of human diseases: it has a major role both in initiation of atherosclerosis (through the adhesion of monocytes to endothelium) and in the development of atherothrombotic event. Monocytes adesion is mediated by leukocytes and endothelial adhesion molecules, such as selectins, integrins, vascular cellular adhesion molecule 1 (VCAM-1) and intercellular adhesion molecule 1 (ICAM-1). Monocytes subsequently migrate through the endothelium in the vascular intima where they accumulate to form the initial lesions of atherosclerosis. In this respect, diabetes is a risk factor for cardiovascular risk and coronary disease: EPA and DHA increase insulin sensitivity and reduce the risk for coronary heart disease. Also rheumatoid arthritis has a strong inflammatory component, which is evidenced through increased interleukin 1, IL-1 [13]. Omega-3 fatty acids reduce IL-1 as well as the number of swollen and tender joints. Supplementation with EPA and DHA and the dietary change in n-6/ n-3 ratio appears to be an effective treatment for these patients associated with traditional therapies. Similarly, it has led to the decrease in the required dose of anti-inflammatory drugs in asthmatic patients. Neoplastic diseases are characterized by inflammation, cell proliferation and high levels of IL-6. In this respect, omega-3 supplementation suppresses IL-6

production: case-control studies in women with breast cancer supported the hypothesis that the balance between n-6 and n-3 in breast adipose tissue plays an important role in breast cancer and its metastasis [14], meliorating both responses to therapy and cancer-associated cachexia [15].

Omega-3 as Antiaging Strategy: effects on Skin and Eyes

The UV exposure causes subcutaneous inflammation with an increase of prostaglandins, cytokines and other pro-inflammatory mediators. The reactive oxygen species (ROS) produce peroxidation of phospholipid membranes and damage to DNA and intracellular proteins. A diet rich of n-3 PUFAs provides photoprotection and contrasts the risk of skin tumors induced by UV [16]: they compete with arachidonic acid (AA) for the metabolism by cyclooxygenases/ lipoxygenases thus decreasing prostaglandins and cytokines [17]. Omega-3 reduce oxidative, inflammatory and vasogenic processes [18]. In this regard, they have been tested in several studies displaying to reduce the symptoms of atopic dermatitis, sunburn, aging and skin infections caused by P. acnes and S. aureus, because of their antimicrobial and anti-inflammatory action [19]. Omega-3 fatty acids also produce an anti-inflammatory action in the lacrimal gland: they increase tear secretion and inhibite the apoptosis of secretory epithelial cells [20]. An higher consumption of omega-3 fatty acid improve the response of anti-inflammatory cytokines, leukotrienes (LTB3) and prostaglandins (PGE3) against the production of arachidonic acid (AA) from diomogamma-linolenic acid (DGLA), which is associated to Dry Eye Disease (DED). Besides the omega-3 EFAs play a significant action in the synthesis of meibum secreted by meibomian glands; their pathway results to attenuate inflammatory products too. People with omega-3 EFA deficiency have a thicker meibomian gland secretion [21]. Moreover omega-3 polyunsaturated fatty acids confer protection against the risk of developing AMD (Age-related Macular Degeneration), since very high levels of DHA are present in the retina, specifically in the disk membranes of the outer segments of photoreceptor cells. A recent meta-analysis of nine epidemiological studies showed a 38% reduced risk for AMD in subjects with high consumption of omega-3 [22]. In fact, both brain and eye tissues are very rich in omega-3 fatty acids and a great number of studies in preterm and full-term human infants suggested that an adequate omega-3 dietary intake is essential for optimal visual development [23,24]. Besides a potential direct effect of these nutrients in the eye, their role could be also mediated by an effect on atherosclerosis and vascular diseases. Moreover, ARM and cardiovascular disease share common risk factors, like smoking, obesity and hypertension, suggesting a contribution of vascular disease to the pathogenesis of AMD [25-27].

Omega-3 and Cardiovascular Health

Mediterranean diet consumption is associated to low prevalence of degenerative and cardiovascular diseases. Low Mediterranean-diet-adherence (MDA) score has been related to high insulin and homeostatic model assessment-insulin resistance levels at birth. The relationship between maternal MDA and offspring lipoprotein profile at birth has been scarcely reported, however a recent cross-sectional study aimed to study the relationship between pregnancy diet quality and serum lipid, arylesterase and homocysteine values at birth: neonates whose mothers consumed low MDA diets presented impaired lipoprotein and increased homocysteine levels at birth [28]. Clinical evidences of omega-3 benefits are strongest against cardiovascular disease. In fact, both Inuit Eskimos, who get high amounts of omega-3 fatty acids from eating fatty fish living in cold sea water, and people following a Mediterranean style diet tend to have increased higher high-density lipoprotein cholesterol (HDL-c) and decreased triglycerides. The relationship between triglycerides (TG), low-density lipoprotein cholesterol (LDL-C) levels, responsible for atherogenic dyslipidemia, and the risk of coronary heart disease (CHD) was firmly established by past landmark studies, but further progresses highlighted omega-3 fatty acids effects on cardiovascular disease (CVD) and lipid parameters. In order to prevent heart diseases, an adequate diet should be low in saturated fat and rich in monounsaturated and polyunsaturated fats, especially omega-3 fatty acids. Clinical evidence suggests that EPA and DHA help reduce cardiovascular risk factors, such as high cholesterol and high blood pressure. Fish oil has been shown to lower levels of triglycerides, and to lower the risk of cardiovascular death, heart attack, stroke, and abnormal heart rhythms in people who have already had a heart attack, preventing ventricular arrhythmias that lead to sudden death [29,30]. Omega-3 fatty acids resulted to be able to make heart cells less excitable modulating ionic channels and also to slower atrioventricular conduction and substantially lower the probability of having a prolonged QT interval [31]. Some studies displayed significant anti-arrhythmic effects in patients with atrial fibrillation who consumed fish oils; however, further studies should clarify this anti-arrhythmic potential [32]. Their anti-inflammatory action could be the key of these beneficial effects: omega-3 decrease pro-inflammatory eicosanoid mediators production from arachidonic acid; on the other side they increase production of anti-inflammatory eicosanoids from EPA; they decrease both chemotactic responses of leukocytes and adhesion molecule expression on leukocytes and on endothelial cells; they also decrease intercellular adhesive interactions. Together, these anti-inflammatory actions may contribute to omega-3 anti-atherogenic effects [33-35], so that fish oil also appears to help prevent and treat atherosclerosis by slowing the development of plaque and blood clots in arteries. Large population studies suggest that getting omega-3 fatty acids in the diet, primarily from fish, helps protect against stroke and

other ischemic accidents. Similarly, clinical studies suggest that diets rich in omega-3 fatty acids lower blood pressure in people with hypertension, which is another main cardiovascular risk factor. An analysis of 16 clinical studies using fish oil supplements found that taking 3 grams of fish oil daily may reduce blood pressure in people with untreated hypertension. Plaque rupture is another dangerous acute event; the plaque contents is exposed to the highly pro-thrombotic environment of vessel lumen [35,36]; this can determine a thrombosis that may lead to myocardial infarction, stroke or other vascular accidents. Ruptures are more frequent where the fibrous cap is thin and partly degraded. Inflammatory cells (macrophages, T cells, mast cells) are there typically abundant, and these cells produce pro-inflammatory molecules making thin and weaken the fibrous cap (the plaque becomes vulnerable and unstable). Omega-3 fatty acids improve atherosclerotic plaques stability by decreasing infiltration of monocytes, macrophages and lymphocytes into the plaques and by decreasing the activity of those cells once they are present into the plaque. Patients taking a fish oil supplements providing 1.4 g EPA + DHA/day, who underwent carotid endoarterectomy were indagated displaying that n-3 fatty acids were incorporated into advanced atherosclerotic lesions and increased plaque stability [37]. In addition, omega-3 also possess antioxidant properties which improve endothelial function and may contribute to their anti-atherosclerotic benefits. Another study in a Japanese population found that high intake of fish was inversely associated with death caused by intracerebral hemorrhage [38]. Evidence to date suggests that DHA is more efficient in decreasing blood pressure, heart rate, platelet aggregation and to improve the endothelial function and the ratio between HDL and LDL cholesterol compared to EPA. These works strongly support the role of omega-3 in decreasing total cardiovascular mortality, so that the daily omega-3 supplementation of 1 g is highly recommended for both primary and secondary prevention of cardiovascular and in particular coronary heart disease. The mechanisms that mediate the cardiovascular protective effects of omega 3 have not been fully elucidated. Anyways cytochrome P450 1A1 efficiently metabolizes n-3 PUFAs to potent vasodilators, thus, we can also hypothesize an increase in nitric oxide (NO)-dependent blood pressure regulation and vasodilation in a CYP1A1-dependent manner [39].

Omega-3 and Metabolic Diseases: Diabetes, Metabolic Syndrome and Non-Alcoholic Fat Liver Disease

Nutritional factors are essentials for metabolic diseases prevention and treatment [40]. In postmenopausal women with metabolic syndrome, dietary intervention plus supplementation of omega-3 resulted in a further decrease in triglycerides and blood pressure and also in an improvement in insulin resistance and inflammatory marker, important components of metabolic syndrome [41]. Diabetic patients often show high triglyceride and low HDL hematic levels. Omega-3 fatty acids from fish oil can help lower triglycerides and apoproteins (markers of diabetes), and raise HDL, so eating foods or taking fish oil supplements may help people with diabetes. Another type of omega-3 fatty acid, ALA from flaxseed, may not have the same benefit as fish oil. In addition, some people with type 2 diabetes may have an increase in fasting blood sugar when taking fish oil. In fact, EPA and DHA intake was shown to improve insulin sensitivity in animal models [42]: in the Seven Countries Study, usual fish consumption resulted to be associated with lower risk of glucose intolerance [40]. Other human studies showed that fish oils reduce the rate of hepatic secretion of very low-density lipoprotein (VLDL). In normolipidemic subjects, n-3 fatty acids prevent and rapidly reverse carbohydrate-induced hypertriglyceridemia [43,44]. While both EPA and DHA decrease fasting and postprandial triglycerides levels, only DHA appears to increase HDL. Another important study involving 41 countries showed that seafood intake might reduce type 2 diabetes mellitus (T2DM) risk in populations with a high prevalence of obesity [45]. Omega-3 tissue levels, such as in plasma and erythrocytes, were reported to be significantly lower in T2DM patients compared with control subjects in case-control studies [46,47]. A very recent systematic review and meta-analysis showed how marine n-3 polyunsaturated fatty acids were inversely associated with risk of type 2 diabetes in Asians, whose T2DM seems to be significantly lower [48]. On the other side, however, mouse models showed an important metabolic interference mediated by heavy metals contaminating seafood: elevated blood methyl mercury levels may interrupt insulin signaling pathways, and decrease plasma insulin and elevate blood glucose levels, thus raising T2DM risk [49-52]. Anyway, omega-3 fatty acids combine positive metabolic actions, primarily mediated by EPA, and anti-inflammatory effects, mostly mediated by DHA. Recent pharmacological studies in Non-Alcoholic Fatty Liver Disease (NAFLD) animal models and in adult humans displayed a lipid profile improvement through lowering triglycerides, a decrease in both insulin-resistance and pro-inflammatory cytokines synthesis [53-55]. Positive results also emerged in childhood: an omega-3 supplement, consisting of DHA 250 mg/day, was administered in a group of 60 NAFLD children for six months; liver steatosis on ultrasound decreased, while triglycerides and insulin resistance markers improved [56]. These studies demonstrate omega-3 anti-inflammatory and insulin-sensitizing properties, suggesting a potential role in prevention and even treatment of NAFLD [57,58] and metabolic syndrome-related conditions [59,60]. In this respect, some randomized trials suggests that wide-range doses (0,81- 3,7g per day) are safe and effective, even if the optimal proportion has not been established yet [61]. In fact, individuals with mixed atherogenic dyslipidemia, type 2 diabetes mellitus and metabolic syndrome are at high risk of developing cardiovascular disease and can often benefit greatly from preventive lifestyle and medical interventions.

Antineoplastic Activity of Omega-3

Many epidemiological studies suggested that a diet rich in omega-3 fatty acids, such as Japanese and Mediterranean diets), is associated with a lower incidence of neoplastic development [62]. Hepatocellular carcinoma risk reduction was dose-dependently evidenced in correlation to fish intake for about 100,000 Japanese patients [63]. Results from an american 22 years prospective study showed a lower risk of colorectal cancer development associated with a higher omega-3 intake [64]), which resulted to be helpful if administrated during chemotherapy too [65]. Omega-3 fatty acids displayed both direct antitumor effects, such as apoptosis induction and angiogenesis and metastasis inhibition, and indirect effects by improving secondary complications associated with cancer, such as cachexia [20]. Supplementation with EPA/DHA increases levels of acetylcholine, and causes a reduction of pro-inflammatory eicosanoids, such as tumor necrosis factor a (TNF-a), Interlukin-1, and Interlukin-6, interfering with arachidonic acid pathway [66]. Murphy et al. in 2011 showed that administration of 2.5 g/day EPA and DHA in patients receiving platinum-based chemotherapy for non-small cell lung cancer determined a two-fold increase in response rate to therapy, in comparison to patients undergoing the same treatment without omega-3 supplementation [67]. A better response to chemotherapy after DHA supplementation was observed also in breast cancer under anthracyclines treatment [68]. These findings reveal that EPA/DHA daily supplementation, during the standard treatment, improved quality of life, physical and cognitive function in neoplastic patients compared to the control group [69]. In addition, a higher prevalence of depression exists in cancer patients (10–30%), compared to general population (5–10%), probably because of an increased production of inflammatory cytokines: this may result in a compliance reduction during therapy and reduced efficacy of various treatments in this group of subjects [70]. In this respect, supplementation with EPA or DHA may alleviate clinical depression because of a reduction of these pro-inflammatory cytokines [71].

Omega-3 and women: localized adiposity and menstrual cycle

Overweight is associated with increased levels of inflammation and metabolic abnormalities, with increased risk of developing insulin resistance, type 2 diabetes, stroke and CVD. Omega-3 can assist in weight loss also reducing the risk of obesity related co-morbidities. These fats can play an important role in the slimming process, especially in female localized slimming, because they have significant vasodilator properties, resulting in increased blood flow in the areas affected by localized adiposity. This mechanism appears to be effective, especially associating with good training of the target area improving the ability to take away the fat released from the cells. In addition, it is possible to observe an increasing cellular oxygenation with better burning of fat in the muscles [72]. Premenstrual syndrome (PMS) and dysmenorrhea are also common problems among reproductive-age women. Abnormal fatty acid metabolism has been implicated in these pathologies. Krill omega-3 supplement showed the ability to reduce breast tenderness, feelings of inadequacy, stress, irritability, depression and joint discomfort. Moreover, these women showed improved energy and well-being, and consumed significantly fewer analgesic medications during the 10 perimenstrual days [73]. Also, polycystic ovary syndrome (PCOS) is very common among reproductive-age women. Omega-3 may be effective in improving hirsutism and insulin resistance in patients with PCOS. In a recent study, Oner et al. demonstrated women treated with daily oral 1,500 mg of omega-3 for six months showed improvement of body mass index (BMI), hirsutism score, insulin and HOMA levels. In the hormonal profile, serum LH and testosterone levels decreased and sex hormone-binding globulin levels increased significantly after six months of therapy [74].

Omega-3 and Nervous system: Development and Neurological Disorders

Dietary supplementation with omega-3 is a safe, economical mean of preventive medicine that has shown protection against several neurologic disorders.Omega-3 fatty acids are highly concentrated in the brain and appear to be important for cognitive (brain memory and performance) and behavioral function. In fact, infants who do not get enough omega-3 fatty acids from their mothers during pregnancy are at risk for developing vision and nerve problems. In particular, EPA and DHA are essential for prenatal and postnatal brain development as well as for the maintenance throughout adult life of cognitive function, behavior management and mood control. In particular DHA is essential for fetal and infant brain development and maturation: it is rapidly stored in brain and retina during the later stages of gestation and early postnatal life [75]. DHA improves visual acuity and eye function in premature newborns. In a full-term neonate, DHA may influence visual acuity too and neural pathways associated with the progression of language acquisition. Since the consumption of omega-3 is essential for the development of the brain and nervous system of children and teenagers, the inclusion of DHA in infant formulas is spreading around the world [76,77]. Recent studies on primates and rodents showed that the adult brain cortex undergoes highly active synaptic turnover throughout life [78] and psychological stress in humans induces the production of pro-inflammatory cytokines, such as interferon gamma, TNF-alpha, IL-6, and IL-10. An imbalance of n-6 and n-3 PUFA in peripheral blood causes an overproduction of pro-inflammatory cytokines. There is evidence that some changes in fatty acid composition, with an imbalance in n-6/n-3 PUFA ratio, are involved in major depression pathogenesis, and that taking omega-3 fatty acids can help depression symptoms: people who took omega-3 fatty acids in addition

to prescription antidepressants had a greater improvement in symptoms than those who took antidepressants alone. In particular, some studies show that omega-3 fatty acid intake helps protect against postpartum depression, among other benefits. Also meta-analysis confirm benefits of omega-3 intake in major depressive disorder (MDD) and bipolar disorder, with promising results in schizophrenia, borderline personality disorder and initial benefits against autistic spectrum [79]. In a clinical study of 30 people with bipolar disorder, those who took fish oil in addition to standard prescription treatments for bipolar disorder for 4 months experienced fewer mood swings and relapse than those who received placebo. Preliminary clinical evidence suggests that people with schizophrenia may have an improvement in symptoms when given omega-3 fatty acids. A number of studies show that reduced intake of omega-3 fatty acids is associated with increased risk of age related cognitive decline or dementia, including Alzheimer's disease. Scientists believe that DHA is protective against Alzheimer's disease and dementia. In fact, accelerated cognitive decline and mild cognitive impairment correlates with low tissue levels of DHA/EPA, and their supplementation seems to improve cognitive function. Studies displayed that EPA and DHA prolonged remission, reducing relapse risk in bipolar disorder patients. High DHA consumption is associated with reduced risk for Alzheimer's disease, although its exact mechanisms and therapeutic potential is not completely clear yet [80]. Another potential application in neurologic field is represented by attention deficit/hyperactivity disorder (ADHD). Children with ADHD may have low levels of essential fatty acids EPA and DHA. In a clinical study of nearly 100 young patients, those with lower levels of omega-3 fatty acids had more learning and behavioral problems, such as temper tantrums and sleep disturbances, than those with normal omega-3 levels. Anyways a few studies have found that omega-3 fatty acids helped improve behavioral symptoms. Even if more research is needed, eating foods that are rich in omega-3 fatty acids is a reasonable approach for ADHD children. Finally, the importance of omega-3 fatty acids in brain function was found also for healthy people [81]: healthy volunteers completed a mood questionnaire and took, such as electroencephalogram and electromyography, were made at baseline. They were divided into two groups consuming either 4 g fish oil a day, providing about 800mg DHA and 1.500 mg EPA, or placebo for 35 days, and after that attention tests, and physiological recordings were repeated. The DHA/EPA group improved significantly on several mood parameters (temper, vigor, anger, anxiety, fatigue, depression, and confusion) and measures of attention but also reaction time resulted to be improved in comparison to placebo group. In addition, dietary supplementation with omega-3 showed to protect against hippocampal neuronal loss after controlled cortical impact and reduced pro-inflammatory response. Interestingly, ω-3 PUFAs prevented the loss of myelin basic protein, preserved the integrity of the myelin sheath, maintained the nerve fiber conductivity and directly protected oligodendrocyte cultures from excitotoxicity [82]. This protective impact of ω-3 PUFAs supports the clinical use of this dietary supplement as a prophylaxis against traumatic brain injury and other nervous system disorders.

Omega-3 and muscle: A Perfect Supplement in both athletes and elderly people

Some studies suggest that omega-3 fatty acids may help increase levels of calcium in the body and improve bone strength, although not all results were positive. Scientific literature also suggest that people who don't get enough of some essential fatty acids (particularly EPA and gamma-linolenic acid, which is an omega-6 fatty acid) are more likely to have greater bone loss than those with normal levels of these nutrients. In a study of women over 65 with osteoporosis, those who took EPA and GLA supplements had less bone loss over 3 years, in comparison to those who took placebo. Many of these women also experienced an increase in bone density. In addition, DHA seem to increase lipid oxidation and insulin sensitivity in skeletal muscle and it can stimulate glycolytic capacity in myocites. Omega-3 resulted to be enhancer of protein synthesis and to promote fat oxidation, thus helping reduce body weight and preventing weight gain. They can probably improve athletic performances, through a modulation on cell membranes permeability and on insulin sensitivity, making the muscle cells more permeable to their necessary nutrients, such as glucose and aminoacids. This is supported by up-regulation of the GLUT4 transporter. Based on these studies, omega-3 appears to be a potent stimulator of metabolism in muscle cells and a potential ergogenic aid [83,84]. Similarly, omega-3 intake may result helpful against elderly sarcopenia too. The age related loss of muscle mass is considered to be largely due to an inadequate response to anabolic stimuli [85]; concurrently, there is the habit of older people to reduce protein intake. A recent interesting study in older adults showed that omega-3 fatty acids supplementation augments both hyperaminoacidemia and hyperinsulinemia, which results to be an anabolic incitement, and induces increase in muscle protein synthesis rate. Omega-3 fatty acids therefore probably attenuate the catabolic trend and may potentially be useful as a therapeutic agent to treat sarcopenia and osteoporosis [86].

Omega-3 and autoimmune/inflammatory diseases: Asthma, Systemic lupus erythematosus and Arthritis

Omega-3 fatty acids can be used as a complementary medicine because of their anti-inflammatory mechanisms of action [87]. Epidemiological studies suggest that dietary omega-3 fatty acids may have beneficial effects on asthma. In fact the low incidence of asthma in Eskimos could derive from their great intake of omega-3 fat fish [88]. A reduction of bronchial inflammation after a omega-3 dietary supplementation was repeatedly reported [89]: a three-week supplementation with 3.2 g of EPA and 2.0 g of DHA reduced eicosanoids and

pro-inflammatory cytokines concentration in the sputum of asthmatic patients [90]. A recent study compared the effects of a widely used anti-LT medication and daily omega-3 supplementation with 3.2 g EPA+ 2.0 g DHA in asthmatic patients for three weeks demonstrated that both fish oil and the anti-LT medication were independently effective in attenuating airway inflammation and hyperpnoea-induced bronchoconstriction [91]. Similarly, six weeks of dietary supplementation with 120 mg/day of omega-3 fatty acids comported a significant improvement in infant bronchial asthma's lung function [92]. Several studies suggest that EPA and fish oil may help reduce some symptoms of other inflammatory diseases, such as Systemic lupus erythematosus (SLE), and some forms of arthritis. SLE is an autoimmune condition characterized by fatigue and joint pain, although fish oil showed to have no effect on lupus nephritis, a frequent kidney complication of the disease. However, most clinical studies examining omega-3 fatty acid supplements have focused on rheumatoid arthritis (RA), another autoimmune inflammatory disease that causes joints phlogosis and pain. Omega-3 effects on antigen presentation, T cell reactivity, inflammatory lipids and peptides and oxygen-derived reactive species production suggest that these fatty acids might have a role in decreasing both risks development and severity in SLE and RA patients [93]. A number of clinical studies and animal models of arthritis have found that fish oil helps reduce symptoms of RA, including joint pain and morning stiffness. One study suggests that people with RA who take fish oil may be able to lower their dose of non-steroidal anti-inflammatory drugs (NSAIDs). In particular, fish oil reduced both arthritis incidence, from 93% to 69%, and severity (mean peak severity score passed from 9.8 to 6.7) of type II collagen-induced arthritis; in addition, arthritis onset resulted to be delayed in mice from 25 days to 34 days [94]. Guidelines for management of early rheumatoid arthritis recommend omega-3 supplementation in order to decrease pain and stiffness in RA patients, as there is excellent evidence to support daily use of up to 6 g omega-3 [95]. Laboratory studies suggest that diets rich in omega-3 fatty acids (and low in the inflammatory omega-6 fatty acids) may also help people with osteoarthritis: New Zealand green lipped mussel (Perna canaliculus), another potential source of omega-3 fatty acids, has been reported to reduce joint stiffness and pain, increase grip strength, and improve walking pace in a small group of people with osteoarthritis. These results suggest that omega-3 fatty acids, along with conventional therapies such as NSAIDs, may help relieve joint pain associated with these conditions.

Conclusions

Omega-3 seem to be one of the most useful supplements for a huge range of the population (premature infants, elderly with sarcopenia, athletes and all the patients with metabolic and inflammatory diseases). Since only the Eskimos, the Japanese and a few other small groups of people do not require these supplements, these fats should be added to foods, rather than be used solely as food supplements. N-3 fatty acids maintain their properties even when packaged in wholesome foods other than fish. Concurrently, omega-6 dietary intake reduction is required, in order to reduce omega-6/omega-3 ratio to the extent provided by the evolution of human biology. There is good evidence from murine and human studies about the Paleolithic diet, the diet of Crete, the Okinawa diet that the physiological n-6: n-3 ratio should be 1:1 or 2:1. Japan has already recommended a ratio of 2:1. The composition of meats, fish and eggs is dependent on animal feed. Fish-meal, flax, and n-3 from algae in animal feeds increase the n-3 fatty acid content of egg yolks and lead to the availability of n-3 fatty acid-enriched eggs in the marketplace. In this respect, other fats are to be consumed in our daily diet: in particular, olive oil increases the incorporation of omega-3 fatty acids in tissues and therefore should always be privileged over any other vegetable oils and animal fats. In the past, industry focused on improvements in food production and processing to increase shelf-life of the products; now and in the future, the focus should be shifted on the nutritional quality of the products in order to improve public health.

Conflict of Interest

The authors declare no conflict of interest.

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