

ω -3 Polyunsaturated Fatty Acids on the Prognosis of Multiple Sclerosis: The Effect of Eicosapentaenoic acid

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Abstract

The effect of nutrition and dietary supplements on the course of multiple sclerosis is a topic of great interest to both patients and clinicians. The influence of ω -3 polyunsaturated fatty acids (PUFAs) on the development and course of multiple sclerosis (MS) has been under investigation. A number of small, uncontrolled clinical trials with fish oil (rich in eicosapentaenoic acid (EPA; 20:5 ω -3) and docosahexaenoic acid (DHA; 22:6 ω -3) have indicated a possible beneficial effects of ω -3 PUFAs, but controlled trials have not been able to draw definitive conclusions. Among ω -3 PUFAs, EPA has the most potent effect on myelinogenesis and inflammatory process, thus the conflicting results could be due to the different mixtures of EPA and DHA contained in the various sources of fish oil. This review discusses on the possible role of EPA in demyelinating diseases.

Keywords: ω -3 polyunsaturated fatty acids; Eicosapentaenoic acid; Docosahexaenoic acid; Multiple sclerosis; Fish oil

Introduction

Multiple sclerosis (MS) is a chronic neurological disease that is a major cause of disability in young adults in Europe and North America [1]. The clinical course of MS is unpredictable and varies individually, with some patients experiencing minimal impairment. The majority of patients have a form of MS referred to as relapsing-remitting MS (RRMS) characterized by periods of clinical stability that are interrupted by relapses. MS is generally considered an immune-mediated disease characterized by disseminated foci of inflammatory demyelination affecting the central nervous system (CNS). Environmental factors have been suggested as possible factors affecting both disease risk and progression in individuals with complex genetic-risk profiles [2].

MS is not yet curable and therapeutic options mainly focus on the control of the autoimmune reaction. The approved therapies include immunomodulatory (interferon-beta (IFN- β), glatiramer acetate) and immunosuppressive agents (fingolimod, azathioprine, mitoxantrone) or antibody mediated (natalizumab) approaches [3]. Although efficacy of all these drugs has been proven in large-scale clinical trials, some major issues still remain unsolved including partial efficacy, considerable variety inpatients response, inconvenience of parenteral application, safety and tolerability aspects, insufficient neuroprotective capacity, and last but not least considerable treatment costs [3]. Against this background the need for an improvement of therapeutic options in MS remains. Identifying therapies that have the potential to alter the disease course with a low side-effect profile are needed.

Complementary and Alternative Medicine Use in MS

There have been a number of studies reporting the prevalence of complementary and alternative medicine (CAM) use by MS patients, and the range of prevalence is quite broad, at 33-70% [4-8]. The majority of MS patients uses CAM as an adjunct to conventional therapies and perceives benefits from both therapies. CAM therapies most frequently employed include diets, ω -3 polyunsaturated fatty acids (PUFAs), antioxidants [9-12].

The role of diet in both causing and ameliorating the severity of MS has intrigued people with MS and researchers alike. One of the first researchers to suggest a relationship between dietary habits and MS was Swank who conducted epidemiological studies of MS in Norway

[13]. He found a lower incidence in the coastal communities with high consumption of fish (rich in ω -3 PUFAs) than in communities where the consumption of animal fat is high. He concluded that a high butterfat intake leads to an increased risk of developing MS, whereas a fish-based diet is associated with a decreased risk of MS. He also developed dietary recommendations based on these findings that were widely used by MS patients before the introduction of disease-modifying therapies in the mid-to-late 1990s.

ω -3 Polyunsaturated Fatty Acids (PUFAs) and Immune Response

ω -3 fatty acids are a range of dietary PUFAs characterized by having a C=C bond starting after the third carbon atom from the methyl end of the carbon chain. The predominant ω -3 fatty acids are α -linolenic acid (ALA; 18:3 ω -3), eicosapentaenoic acid (EPA; 20:5 ω -3) and docosahexaenoic acid (DHA; 22:6 ω -3) and are classified as essential fatty acids in humans because they are a requirement for the maintenance of health and cannot be synthesized *de novo*, although limited conversion of ALA to the longer chain fatty acids, EPA and DHA can occur, particularly in men [14,15]. Algae are the primary natural source of EPA and DHA, and as a result of their consumption and dietary accumulation, fish are a rich source of these fatty acids.

Both human and animal studies have proved that diets high in EPA and DHA can increase the proportion of these PUFAs in cell membranes and also reduce the levels of arachidonic acid (AA, C20:4 ω -6), a stress-related biomarker [16]. EPA and DHA are able to inhibit partly a number of aspects of inflammation including leucocyte chemotaxis, adhesion molecule expression and leucocyte-endothelial adhesive interactions,

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production of inflammatory cytokines and T cell reactivity. These ω -3 PUFAs function through a variety of mechanisms, including via cell surface (GPR120) and intracellular NRC3 (i.e. PPAR- γ) receptors that control inflammatory cell signaling and gene expression patterns [17]. In addition, ω -3 PUFAs can modify the production of lipid mediators. This occurs through several mechanisms that are all related to the fatty acid composition of cell membrane phospholipids: 1) the decreased amount of AA results in decreased production of eicosanoids like series-2 prostaglandins (PGs) and 4-series leukotrienes (LTs) from inflammatory cells; 2) EPA acts as an alternative substrate for cyclooxygenase (COX) and lipoxygenases (LOX) enzymes, giving rise to 3-series PGs and thromboxanes (TXs) and 5-series LTs. The difference between ω -3 and ω -6 fatty acid-derived eicosanoids is that most of the mediators formed from EPA and DHA are anti-inflammatory, whereas those formed from AA are pro-inflammatory or show other disease-propagating effects [18]. Furthermore, EPA and DHA also give rise to resolvins (from EPA and DHA) and neuroprotectins (from DHA) through pathways involving COX and LOX enzymes [19,20]. Among ω -3 PUFAs, EPA appears to have the most potent effects on immune response [21,22]. Moreover, recent studies provided evidence that one effect of EPA may involve induction of CD4+CD25+ regulatory T cells (Tregs) [23] that appear to be critical in regulating immune response to self-antigens.

ω -3 PUFAs and Multiple Sclerosis

The immune modulator and anti-inflammatory effects of ω -3 PUFAs have been suggested as rationale for their potential therapeutic use in patients with MS.

Clinical trials related to ω -3 PUFAs supplementation pointed out some benefits for RRMS. The largest study, with over 300 patients, used 10 g fish oil supplementation as the intervention and olive oil as placebo [24]. Although not statistically significant difference was observed, there was a trend favoring the ω -3 PUFAs group, with fewer people progressing one point on the Expanded Disability Status Scale (EDSS). Beneficial trends on decreasing the duration and the frequency of MS relapses in favor of treatment group were also observed.

An open-label study [25] showed that ω -3 PUFAs supplementation (6 g/day of fish oil; 86% EPA+DHA) for 6 months in MS patients and healthy controls decreases the levels of interleukin-1 β (IL-1 β), tumor necrosis factor- α (TNF- α), IL-2, and IFN- β produced from unstimulated and stimulated peripheral blood mononuclear cells (PBMC) as well as reduces the secretion of the inflammatory eicosanoids, prostaglandin E2 and leukotrienes LTB4, which are known to be increased in MS patients [26]. Weinstock-Guttman et al. [27] investigated fish oil and other dietary fat changes as a treatment

among users of approved MS conventional therapies. In a randomized, double-blind, placebo-controlled study a significant improvement in quality of life (physical and mental health components) was observed in participants receiving a low saturated fat diet and ω -3 PUFAs supplementation (6 g/day of fish oil; 65% EPA +DHA) at 6 months (Table 1). In this study no changes in plasma inflammatory cytokine levels were observed. The difference in outcomes on inflammatory cytokine levels between Weinstock-Guttman et al. and Gallai et al. studies can be due to the different concentrations of EPA and DHA evaluated (Weinstock-Guttman et al. evaluated a lower concentration than Gallai et al.) and different specimen used in cytokine measures (plasma versus immune cell secreted). Despite these differences, both studies reported positive effects of ω -3 PUFA supplementation in MS. However, the potential therapeutic effect related to a low fat diet cannot be clearly excluded in this last study.

In a multicenter, randomized, placebo-controlled trial, in which 92 patients with RRMS received either fish oil (5 g/day; 60% EPA +DHA) or placebo, no significant difference was found in either the number of lesions on gadolinium-enhanced magnetic resonance imaging (MRI) at 6 months or the relapse rate at 6 or 24 months [28]. Furthermore, no differences were detected in disability progression, fatigue or quality-of-life scores. However, no dietary restrictions or recommendations were given to participants, which might have attenuated any benefit of the fatty acid supplementation.

Swank and Goodwin [29] conducted a 35-year long, non-randomized, retrospective study in MS patients and found that a diet with very low saturated fat content (average saturated fat 15-17 g/day) supplemented with cod liver or vegetable oils (10-40 g/day) provided long term benefits on mortality, relapse severity and disability, particularly if initiated during the earliest stages of MS. Although this study is a unique long-term follow-up of an intervention for MS, it has been criticized for the lack of a control group for comparison for scientific validation.

Recently, Pantzaris et al. [30] showed in a randomized, double-blind, placebo-controlled clinical trial that the administration of ω -3 (EPA 1.65 g/day and DHA 4.65 g/day) and ω -6 fatty acids with vitamins reduce the annualized relapse rate in RRMS. However, in this study it is not possible to discriminate the effects of ω -3 and ω -6 fatty acids.

The available data are insufficient to assess the real effect of these compounds in MS. In addition high dropout rates limit the conclusions that can be drawn from these studies. Given positive trends observed in small studies, the potential of ω -3 PUFAs to slow the disease course should be evaluated further. Among ω -3 PUFAs, EPA has the most potent effect on inflammatory processes [31,32] and the conflicting

Author	Patients	Type of study	Intervention	n	Main results
Bates (1989) [24]	RRMS	RCT, double blind parallel design;	EPA 1.71/DHA 1.14g/day vs. Oleic acid 7.2g/day	145 147	No Significant effect on relapse rate and disability progression. Positive trend in fish oil group
Weinstock-Guttman (2005) [27]	RRMS	RCT, double blind parallel design; 12 month follow-up. IMT allowed	EPA 1.98/DHA 1.32 g/day+dietary fat restriction Vs. Olive oil 6 g/day+dietary fat restriction	13 14	No effect on relapse rate or disability. Positive effect on mental and physical health related to quality of life in fish oil group
Torkildsen (2012) [28]	RRMS	RCT, double blind parallel design; 24 month follow-up	EPA 1.35/DHA 0.85 g/day vs. Corn oil 5 g/day	46 46	No effect of ω -3 PUFAs on MRI-activity, relapse rate or disability progression neither as monotherapy nor as add-on to IFN- β
Pantzaris (2013) [30]	RRMS	RCT, double blind parallel design; 30 month follow-up	EPA 1.65/DHA 4.65 g/day GLA 2.0/LA 3.85 g/day+vit A, vit E, γ -tocopherol (0.6, 22, and 760 mg/day) vs. Olive oil 16.9 g/day	20 20	Significant reduction of the annual relapse rate and disability progression

Table 1: Randomized controlled trials of ω -3 PUFAs in MS.

results obtained in different clinical trials could be due to the fact that fish oils from different sources contain variable mixtures of EPA and DHA.

EPA and Myelin Gene Expression

In addition to having anti-inflammatory properties, ω -3 PUFAs have proved to have beneficial effects on myelinogenesis. In an *in vitro* study, Van Meeteren showed that the supplementation of oligodendroglia cells with ω -3 PUFAs increased their degree of differentiation [33]. In our *in vitro* experimental model using transfected C6 glioma cells with proteolipid protein (PLP) promoter [34], we showed that EPA stimulates PLP gene expression via cAMP mediated pathways. Afterwards, to verify whether the ω -3 PUFAs have an *in vivo* role on the myelinogenesis process, a single dose of EPA or DHA was injected into brains of rat pups, and myelin development was assessed 3 days later by evaluating myelin protein expression in medulla, cerebellum, and cortex. Our results showed that the levels of PLP, myelin basic protein, and myelin oligodendrocyte protein mRNAs increased in nearly all brain regions of DHA and EPA treated animals, but the effect was more pronounced in EPA treated rats. The enhancement in PLP transcript levels was followed by an increase in PLP translation in EPA treated rats. A further indicator of accelerated myelination was the increase in 2-3-cyclic nucleotide 3-phosphodiesterase (myelin marker) protein levels [35].

In MS treatment, the enhancement of endogenous remyelination represents an attractive therapeutic goal. Spontaneous and robust remyelination occurs at the early stages of MS. However, remyelination is incomplete - i.e., faithful reconstruction is not fully attained, originating a thinner and shorter myelin sheath. As the disease progresses, eventually remyelination completely fails. The reasons for this inadequacy are unknown, as the oligodendrocyte precursor cells (OPCs), the cell population that is considered to be the most important source of remyelinating oligodendrocytes in the adult CNS, are present in early demyelinating lesions in MS.

There are many possible speculative explanations for remyelination failure in MS, including quantitatively inadequate recruitment and/or differentiation of OPCs; axons not receptive to remyelination; and inappropriate support of growth factors by astrocytes and/or other inflammatory cells, such as the extracellular microenvironment with regard to matrix proteins and adhesion molecules [36]. Thus, extensive studies are under way to identify factors involved in OPC differentiation during remyelination. It is generally accepted that the process of remyelination represents a recapitulation of myelination during development, and so the key factors affecting the developmental maturation of OPCs into myelinating oligodendrocytes also should favor remyelination in the adult CNS.

Thus, in addition to ω -3 PUFA effect on decreasing proinflammatory cytokines levels, there is evidence supporting ω -3 PUFAs effect in myelin genes both *in vitro* and *in vivo* and EPA has the major effect.

EPA and Experimental Allergic Encephalomyelitis

The effects of EPA were investigated in EAE induced in dark agouti (DA) rat which develops a severe and protracted encephalitis and wide demyelination [37,38]. In the DA rat EAE model, following the first attack and remission, animals experience pathology similar to MS patients with T cells, macrophages, glial cells and, additionally, autoantibody-producing plasma cells involving in demyelination axonal loss spreading beyond the spinal cord into the cerebellum. Most of the animals also relapse; thus the similarity of disease in the

DA rat EAE model to the human disease renders this strain a valid and useful model for testing potential MS therapies. We observed that prophylactic administration of EPA conferred significant protection against development of EAE [39]. The protective role was manifested at clinical, histological and molecular levels. In particular, we observed a delayed onset of clinical severity of disease in rats fed EPA-supplemented diets that were associated to an increased expression of myelin proteins and an improved integrity of the myelin sheath. The increased expression of NG2-chondroitin sulfate proteoglycan (OPCs marker) and PLP protein levels observed in treated rats suggests that EPA improves myelin self-repair capability by unblocking OPCs and pushing them toward becoming mature myelinating OLs. Thus EPA seems to reach a major goal of MS therapy: to overcome the remyelination failure.

Moreover, an up-regulation of expression of fork head transcription factor (Foxp3, the most specific marker for Treg cells) in the CNS of EPA feeding rats during the acute phase of EAE was observed. Tregs are capable of controlling the development and activity of pathogenic effector T cells during autoimmune diseases through cell-to-cell contact or cytokine-dependent pathways, respectively [40]. Defective Treg function may be important in the pathogenesis of MS as well as in its rodent models [41,42]. For example, targeted deletion of Tregs causes spontaneous autoimmune disease in mice, whereas augmentation of Treg function can prevent the development or alleviate variants of EAE [43].

Based on evidences that EPA could have beneficial and protective effects directly on oligodendrocytes, we have evaluated the effects of EPA in the MS model characterized by toxic demyelination induced by cuprizone (CPZ). CPZ feeding, with mechanisms not yet well established, induces oligodendrocyte degeneration, disruption of myelin sheath and demyelination mainly localized in the medial corpus callosum (CC) [44]. In our study, EPA was daily administered by gavage to newborn rats for 21 days, and then they were fed for 9 days on the CPZ diet. The results showed that EPA was able to partially protect the brain against damage induced by CPZ intoxication [45].

Conclusion

In summary, EPA may have a potential benefit in MS for its immunomodulatory and neuroprotective properties. In fact, pathological demyelination and the corresponding repair mechanism requires a finely orchestrated interplay between the inflammatory immune cells that mediate the damage but also stimulate myelin repair by oligodendrocyte precursor cells. Evidence on the possible benefits of EPA in MS is lacking. Previous published trials were focused on the effect of fish oil on MS. The conflicting results reported in literature could be due to the different mixture of EPA and DHA present in the different sources of fish oil so that the EPA amount could be too low to exert a therapeutic action. Further studies should be designed to evaluate the effectiveness of EPA both as monotherapy and in combination with disease-modifying drugs in MS.

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