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NEUROLOGICAL DISEASES AND OMEGA 3 FATTY ACIDS

OMEGA-3 MASNE KISELINE U NEUROLOŠKIM BOLESTIMA

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Abstract *Omega-3 long chain polyunsaturated fatty acids (LC-PUFAs) are essential fatty acids necessary for normal cell membrane function, that are defficient in contemporary diet. They have anti-inflammatory properties and are involved in gene expression, cellular signaling and membrane organization. Omega-3 LC-PUFAs are involved in stimulaton of blood circulation, increase in the breakdown of fibrin, and also may reduce blood pressure, and given in food can significant decrease the thickness of the carotid arteries. Supplements with omega-3 fatty acids can help control seizures in pharmacoresistent epilepsy. Higher intake of omega-3 PUFAs can lower relative risk of dementia incidence or progression and improve memory in healty elderly volunteers. Higher fish intake was found to lower risk for multiple sclerosis and arrest its progression. Favourable effects are also found in Huntington's disease and headache.*

Key words: *omega-3 fatty acids, polyunsaturated fatty acids, dementia, epilepsy, multiple sclerosis*

Sažetak *Omega-3 polinezasićene masne kiseline dugih lanaca (LC-PUFAs) su esencijalne masne kiseline neophodne za normalno funkcionisanje ćelijske membrane, i koje su u savremenoj ishrani deficijentne. Ove masne kiseline imaju anti-inflamatorna svojstva i uključene su u genske ekspresije, celularnu signalizaciju i organizaciju membrane. Omega-3 LC-PUFAs su uključene u stimulaciju cirkulacije, povećanje razgradnje fibrin, a takođe mogu da smanje krvni pritisak i date u hrani mogu da značajno smanje debljinu zida karotidnih arterija. Suplementi sa omega-3 masnim kiselinama mogu da pomognu u kontroli napada farmakorezistentne epilepsije. Veći unos omega-3 PUFAs može da smanji relativni rizik od demencije ili učestalost napredovanja i da poboljša memoriju zdravih starijih volontera. Pronađeno je da viši unos ribe može da smanji rizik za oboljevanje od multiple skleroze i zaustavi njeno napredovanje. Povoljni efekti se takođe mogu naći u Hantingtonovoj bolesti i glavoboljama.*

Ključne reči: *omega-3 masne kiseline, polinezasićene masne kiseline, demencija, epilepsija, multipla skleroza*

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INTRODUCTION

Since the mid-19th Century in the industrial world there has been a significant decrease in vital micronutrients, such as omega-3 polyunsaturated fatty acids, and an increase in other fats, most notably omega-6 fatty acids compared with traditional diets rich in fish, wild game and leaves (1). The modern diet is emphasizing grains, dairy products and grain-fed meats with increases in total fat, saturated fat and linoleic acid (2). The increase in the consumption of ω-6 fatty acids and a marked reduction in the consumption of ω-3 fatty acids in western societies led to an imbalance in the ω-6/ω-3 ratio much different from the 1:1 ratio of humans in the past (and wild animals of past and present times) resulting in ω-6/ω-3 ratios in the range of up to 20-30:1 (3). The modern diet has significant caloric intake of predominantly fats, above the recommended 30-35% with a high proportion of saturated fats (> 10%), rich in ω-6 and a low proportion of ω-3 fatty acids.

OMEGA 3 FATTY ACIDS

Omega-3 and omega-6 fatty acids are long-chain polyunsaturated fatty acids (LC-PUFAs) present in fish and plants. Omega-3 LC-PUFAs are comprised of 20 or more carbon atoms and three or more double bonds (4). These oils are classified as omega-3 or omega-6 according to the location of the last double bond in relation to the terminal methyl end of the molecule. The carbon chain has the acid (COOH) end and the methyl (CH3) end. The location of the first double bond is counted from the methyl end, known also as the omega (ω) or n end. In the omega-6 fatty acids, the first double bond is between the 6th and 7th carbon atoms and for the omega-3 fatty acids the first double bond is between the 3rd and 4th (5).

The parental molecules are **α-linolenic acid** (ALA, 18:3n-3) which is "short-chain" eighteen-carbon n−3 fatty acid for n-3 fatty acids and **linoleic acid** (LA) among n-6 fatty acids. Through a process of enzymatic desaturation and elongation ALA is converted to LC-PUFA: eicosapentaenoic acid (EPA, 20:5n-3), which may in turn be converted to docosahexaenoic acid (DHA, 22:6n-3) in the omega-3 series while the linoleic acid (LNA) is converted to arachidonic acid (AA) in the omega-6 series (6). These fatty acids are metabolized in the liver. α-linolenic acid and linoleic acid are **essential** fatty acids and can only be obtained from external sources and can not be synthesized in the human organism. These acids are vital for normal metabolism. Fatty acids in the omega-3 and omega-6 series cannot be interconverted. An important point is that ALA is and essential nutrient but EPA and DHA are not efficiently produced in human organism from ALA, so additional external sources of these two LC-PUFA are needed for optimal level. The family of omega 3 fatty acids is made up of 8 components.

The total omega-3 fatty acids are associated with lower levels of pro-inflammatory markers (IL-6, IL-1ra, tumor necrosis factor-a - TNFa, CRP) and higher anti-inflammatory markers (soluble IL-6r, IL-10, transforming growth factor-a - TGFa) (7). If both *n*−3 and *n*−6 fatty acids are present, they will "compete" to be transformed, especially important for the formation of thromboxane a factor important for the aggregation of platelets. The leukotrienes are important in immune/inflammatory-system response involved in etiopathogenesis of arthritis, systemic lupus, asthma and recovery from infections.

Fatty acids released from membrane phospholipids by cellular phospholipases, or those from the diet are important cell signaling molecules acting as second messengers of the inositide phospholipid and the cyclic AMP signal transduction pathways (8). Fatty acids also rapidly and directly alter the transcription of specific genes involved in inflammation (9).

EPA and DHA participate in diverse biologic activities thought to be beneficial to human health. It is supposed that majority of positive effects of omega-3 oils is dependent on immune-modulating activities, via the mechanisms of gene expression, cellular signaling and membrane organization (10). The omega-3 and omega-6 LC-PUFA are precursors of eicosanoids, such as prostaglandins, leukotrienes, isoprostanes, lipoxins and thromboxanes (11).

Dietary DHA is incorporated into cell membranes resulting in increased fluidity and permeability affecting cellular signaling determining the binding

or release of neurotransmitters (12). Omega-3 fatty acids also have pro- and anti-apoptotic features, depending on the tissue. Antiapoptotic properties of DHA metabolites are documented in human retinal pigment epithelial cells (13). On the other end, in several neoplastic disorders, DHA may exert antineoplastic properties by promoting tumor cell apoptosis (13).

The polyunsaturated fatty acid content changes fluidity inside the membranes-pacemaker making possible the activities of membrane-bound enzymes, receptors, transporters and other catalytic molecules. DHA in neuronal membranes enhances synaptic membrane fluidity and function, and is involved in regulation of gene expression, cell signaling, and in the electrical basis for memory formation (14).

The DHA and EPA content of cell membranes depends on current dietary intakes. Within the cell membrane, there is a dynamic mechanism of the fatty acids attached to phospholipids that are constantly being fine tuned by enzymes (acyltransferases) that remove DHA and EPA from the tails of certain phospholipids and reposition them to others (15).

OMEGA 3 FATTY ACIDS IN NEUROLOGICAL DISEASES

Vascular diseases

Chronic inflammation has been found to contribute in development of cardiovascular disease, stroke, and rheumatoid arthritis (16). LC-PUFA may stimulate blood circulation, increase the breakdown of fibrin, and may reduce blood pressure. One of the possible mechanisms of vascular protection is antidiabetic affect of EPA and DHA, but mostly of ALA maybe through improving insulin sensitivity (17).

It was shown that patients with unhealthy blood sugar levels given the EPA had a statistically significant decrease in the thickness of the carotid arteries, along with improvement in blood flow (18). A large study confirmed that five years of receiving EPA compared to statin drug showed that patients in EPA group had better cardiovascular function with reduction of nonfatal coronary events (19).

Another important issue is the ω-6/ω-3 ratio, as its good balance is important for the prevention and treatment of cardiovascular diseases (1). For the secondary prevention of cardiovascular disease, a ratio of 4:1 has been associated with a 70% reduction in total mortality. The optimum ratio was determined as 4:1-5:1 without exceeding 10:1 (20). In the view of other negative studies of ratio importance, it has been recommended that humans has to increase the intake of both ω-6 and ω-3 (more so) on daily basis as current foods are deficient in both (21).

Epilepsy

In spite of prolific development of new antiepileptic drugs still 20-30% patients are drug resistant and continue to have seizures frequently and 1 in 1000 patients with chronic epilepsy will die with no apparent reason the so called sudden unexplained death in epilepsy (SUDEP) (22). There are some evidence from experimental and clinical studies that omega-3 fatty acids can control their seizures and hence SUDEP. The safety of omega-3 supplementation in people with epilepsy has been proven (23).

PUFAs are main constituents of membrane phospholipids in brain tissue playing important roles in sleep induction, long term potentiation, spatial learning, synaptic plasticity, resolution of inflammation and neuroprotection (24).

Chronic treatment with omega-3 supports neuroprotection and positive plastic changes in the brain of rats with epilepsy, with a reduction in neuronal death in CA1 and CA3 areas of the hippocampus which could be attributed to n-3 PUFAs ion channel modulation, and anti-inflammatory action while in in vitro studies DHA showed inhibition of epileptiform activity and synaptic transmission mainly through the frequency-dependent blockade of Na+ channels in the rat hippocampus, and stabilizing neuronal membrane by suppressing voltage-gated Ca2+ currents and Na+ channels (22).

Dementia and cognitive decline

Even in healthy subjects DHA and EPA can improve cognitive performance. In a study among

volunteers ages 22-51 years consuming either 4 g fish oil/day (providing 800 mg DHA and 1,600 mg EPA) or 4 g olive oil as placebo, the DHA/EPA group improved significantly over placebo on: vigor, anger, anxiety, fatigue, depression, confusion, reaction time, sustained attention and a significant reduction in errors on the attention test (25). A small study was done of phophatidylserine-containing omega-3 daily supplementation in eight elderly volunteers with subjective memory complaints. This supplementation resulted in 42% increase in delayed recall of words (26).

Recent epidemiological studies revealed a positive correlation between relatively high DHA and EPA intake and lower relative risk of dementia incidence or progression. In the Rotterdam Study fish consumption was inversely related to dementia incidence and more specifically to the risk of developing Alzheimer's disease (27). The Zutphen Elderly Study, demonstrated that fish consumption was inversely associated with cognitive impairment at baseline, and after three years, as with the Rotterdam study, high fish consumption was inversely associated with cognitive decline but omega-3 intake did not correlate with either measure (28). After six years, Rotterdam Study data concluded that low intake of omega-3 fatty acids was not associated with increased risk for dementia (29) while the analysis after five years of the Zutphen Elderly Study data confirmed that consumers of fish had a statistically significant decrease in cognitive decline with higher the intake of DHA/EPA (an average of 400 mg fish omega-3s per day) being connected to this effect (30). In a Chicago community study, residents ages 65-94 were evaluated via a self-reported food questionnaire and tracked for an average 3.9 years (31). Those who consumed a fish meal once weekly had a statistically significant 60-percent decreased risk of Alzheimer's disease, compared with those who rarely or never ate fish.

As part of the U.S. Framingham Heart Study, a subcohort of elderly subjects who were free of dementia at baseline, were followed for a mean 9.1 years for development of all-cause dementia and Alzheimer's disease (32). After controlling for other variables, subjects in the upper quartile of plasma phospholipid fraction DHA levels (mean DHA intake of 180 mg/day and a mean fish intake of 3.0 servings per week) had approximately half the relative risk of developing all-cause dementia compared to subjects in the three lower quartiles.

Many characteristics of n-3 fatty acids make them an interesting agent in treating Alzheimer's disease (33). Studies done till now are not encouraging. Dietary intake of n-3 fatty acids did not differ among demented and nondemented subjects (34). Some cognitive benefits (learning and memory) were found in very mild cognitive impairment subjects treated with DHA of algal origin, but not in mild to moderate Alzheimer's disease (35). More research is needed in omega 3 fatty acids influence on prevention and treatment of dementia.

In the Atherosclerosis Risk in Communities Study older middle aged participants were longitudinally followed up and repeatedly tested for word recall, psychomotor speed and verbal fluency (36). Higher plasma omega-3 fatty acids levels were linked to reduced risk for deterioration in verbal fluency, particularly in subjects with dyslipidemias and hypertension. It was found that the brains of Alzheimer's disease patients have less DHA in the gray matter than individuals without Alzheimer's disease at autopsy (37). Individuals with mild cognitive impairment have abnormally low blood levels of DHA and EPA (38).

In a double-blind randomized controlled trial, patients with mild-to-moderate Alzheimer's disease receiving DHA and EPA daily or a placebo for six months, and after that the DHA/EPA supplements for six more months, decline in cognitive function did not differ between groups, but in a subgroup with less severe cognitive dysfunction a significantly slower decline was observed in the DHA/EPA group (39). A similar positive effect was noticed in the placebo group after crossover to DHA/EPA for the second six months. The same group reported significant improvement of agitation in apolipoprotein E4 (APOE4) carriers and improvement of depression in non-APOE4 carriers on omega-3 supplementation (40).

Multiple sclerosis

Coastal Norwegian residents with higher fish and less animal fat intake had lowered risk for multiple

sclerosis in the study of Swank and collaborators (41). Patients instructed to limit animal fat consumption and supplement with cod liver oil (5 g/day) and have three fish meals per week, over 35 years, experienced a much lower rate of progression to advanced MS and lower death rate than control subjects (42). Also, patients on the restricted diet in early disease, prior to developing disability, 95 percent had not progressed.

Huntington's disease

A purified EPA in its ethyl ester form ("ethyl-EPA") in a small randomized controlled trial with advanced Hungtington' disease showed improvement of the orofacial dyskinesia and less brain atrophy over placebo and in a larger study a suspicion was raised that it is a mixture of EPA and DHA, and not a purified EPA, that might have been more effective (43).

Headache

High intakes of n-6 PUFAs, LA and AA may provoke physical pain increasing their metabolism in immune and nervous tissue, making it a possible mechanism of chronic daily headache (44). AA can directly potentiate N-methyl-d-aspartate (NMDA) receptor currents as well as being the precursor of various neuroactive and vasoactive compounds that are relevant to pain processing. Increased omega-3 dietary intake is a possible adjuvant factor in treating this type of headache but it waits confirmation from clinical studies.

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