

Omega-3 polyunsaturated fatty acids and cardiovascular diseases

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Abstract. The article presents some general facts about omega-3 fatty acids and their role in the treatment and prevention of cardiovascular diseases. Omega-3 fatty acids are essential for the human body. Their beneficial effects in the prevention of cardiovascular disease have been known for decades. Since then, several epidemiological and interventional trials showed the value of omega-3 acids in the treatment of certain diseases. Most of them revealed the protective role of omega-3 fatty acids on heart and cardiac functions. However, some of these studies couldn't demonstrate a positive association between fish oils and preventing cardiac events. The major cardiologic societies from European Union and United States of America recommend omega-3 fatty acids as supplements for primary and secondary prophylaxis of cardiovascular diseases.

Key Words: omega-3 fatty acids, cardiovascular diseases, protective factor, diet recommendations.

Resumen. El artículo presenta datos generales sobre ácidos grasos omega-3 y sus papel en el tratamiento y en la prevención de las enfermedades cardiovasculares. Los ácidos grasos omega-3 son esenciales para el cuerpo humano. Sus efectos benéficos en la prevención de las enfermedades cardiovasculares son conocidos desde decenios. Desde entonces, unas pruebas epidemiológicas y terapéuticas enseñaron la importancia de los ácidos grasos omega-3 en los tratamiento de algunas enfermedades. La mayoría han relevado el papel protector de los ácidos grasos omega-3 sobre la corazón y sobre sus funciones circulatorias. Otros estudios no han señalado una relación entre el aceite de pescado y la prevención de los casos de infarto. Las más importantes asociaciones de cardiología de la Unión Europea y de los Estados Unidos recomiendan la utilización de los ácidos grasos omega-3 como suplemento en la prevención primaria y secundaria de las enfermedades cardiovasculares.

Palabras claves: ácidos grasos omega-3, enfermedades cardiovasculares, factor protector, recomendaciones nutricionales.

Rezumat. Articolul prezintă câteva date generale despre acizii grași omega-3 și rolul lor în tratamentul și prevenirea bolilor cardiovasculare. Acizii grași omega-3 sunt esențiali pentru corpul uman. Efectele lor benefice în prevenirea bolilor cardiovasculare sunt cunoscute de câteva decenii. De atunci, câteva trialuri epidemiologice și intervenționale au arătat valoarea acizilor omega-3 în tratamentul unor boli. Majoritatea au relevat rolul protector al acizilor omega-3 asupra inimii și funcției circulatorii. Altele nu au găsit o corelație între uleiul de pește și prevenirea evenimentelor cardiace. Societățile mari de cardiologie din Uniunea Europeană și Statele Unite ale Americii recomandă acizii grași omega-3 ca și supliment în profilaxia primară și secundară a bolilor cardiovasculare.

Cuvinte cheie: acizi grași omega-3, boli cardiovasculare, factor protector, recomandări alimentare.

Introduction. Omega-3 (n-3) fatty acids are a family of polyunsaturated fatty acids (PUFAs) that have in common a carbon-carbon double bond in the n-3 position. The major sources of omega-3 fatty acids are fish oils (EPA - eicosapentaenoic acid, DHA - docosahexaenoic acid) and plants (ALA - α -linolenic acid). ALA was first isolated from hempseed oil in 1887 (Deuel 1951). In 1970, the results of a study on the Eskimo population in North-Western Greenland revealed a lower concentration in seric cholesterol and triglycerides, as compared to Danish controls. The major finding was the replacement of omega-6 fatty acids with omega-3 fatty acids (Bang et al 1971). Several years later, a study linked this replacement to the Eskimo's diet, which consisted mainly in fish (Bang et al 1976). The benefits of a diet based on fish are explained by the rich

intake in very long chain, highly polyunsaturated omega-3 fatty acids (EPA and DHA). Since then, several trials studied the effect of omega-3 fatty acids on various pathologies.

General information. Omega-3 fatty acids are essential for the human body, which cannot synthesize them *de novo*. There are three important omega-3 fatty acids: α -linolenic acid [(ALA), 18 carbons, 3 double bonds], eicosapentaenoic acid [(EPA), 20 carbons, 5 double bonds] and docosahexaenoic acid [(DHA), 22 carbons, 6 double bonds]. ALA is an essential fatty acid because it cannot be synthesized in the human body from saturated fatty acids, n-9 monounsaturated fatty acids, or n-6 polyunsaturated fatty acids (PUFAs). Humans lack the desaturase that inserts a double bond at the C-15 position of a fatty acid carbon chain (Gebauer et al 2006). EPA and DHA are synthesized in the human body from ALA but with relatively low conversions so that diet is the main source also for these two fatty acids.

Omega-3 and omega-6 acids are essential for normal growth and development of the human body. Omega-6 fatty acids contain a carbon-carbon double bond between the 6th and 7th carbon atoms from the methyl end of the fatty acid. An insufficient intake of omega-3 acids may lead to hemorrhagic dermatitis, hemorrhagic folliculitis, impaired wound healing, growth retardation. These fatty acids are found in high concentration in the brain and are important for memory, physic performance and behavior. Newborns from mothers who do not get enough omega-3 acids during pregnancy, are susceptible to develop vision and nervous system problems. In addition, there have been several studies that proved the beneficial effect of the consumption of omega-3 fatty acids on cardiovascular diseases, psychiatric disorders, cancer and other conditions. Omega-3 and omega-6 fatty acids compete for the same enzymes. A balance between the intake of omega-3 and omega-6 fatty acids is necessary for maximizing the benefits of these fats. High levels of omega-6 fatty acids are dangerous because they increase the probability of cardiovascular diseases. Omega-3 fatty acids help to reduce inflammation, and omega-6 acids promote the inflammation. The typical Western diet includes a ratio of omega-6 to omega-3 of 10:1. The optimal ratio is closer to 4:1 (Simopoulos 2002).

EPA and DHA are found in cold-water fish such as tuna, sprat, mackerel, herring, anchovy, salmon, sardines and cod (see Table 1). Fish get their EPA and DHA from marine algae (Brunner et al 2008). ALA is found in flaxseeds, flaxseed oil, rapeseed oil, soybeans, soybean oil, pumpkins seeds, perilla seed oil, walnuts, and black raspberries. Microalgae *Cryptocodinium cohnii* and *Schizochytrium* are rich sources of DHA, but poor sources of EPA (see Table 2 for vegetal sources of omega-3 fatty acids).

Table 1

Fish sources of omega-3 fatty acids.
Serving size: 100 g, cooked

Fish	EPA + DHA content (g/Serving)	Calories/Serving
Farmed salmon	2.15	206
Atlantic herring	2.01	203
Wild salmon	1.84	182
Sardine, canned in tomato sauce	1.35	186
Atlantic mackerel	1.20	262
Farmed rainbow trout	1.15	169
Wild rainbow trout	0.98	150
White tuna, canned in water	0.86	128
Halibut	0.47	140
Shrimp	0.32	99
Fresh yellowfin tuna	0.28	139
Light tuna, canned in water	0.27	116
Atlantic cod	0.16	105

Sources: www.nal.usda.gov/fnic/foodcomp/search, www.nutritiondata.com, U.S. Food and Drug Administration.

Cardiovascular implications of omega-3 fatty acids. Since 1970, several trials studied the effects of omega-3 fatty acids on various diseases with some degree of success: cardiovascular illnesses, diabetes, obesity, hypercholesterolemia, rheumatoid arthritis, osteoporosis, depression, bipolar disorders, schizophrenia, attention deficit/hyperactivity disorder, burns, inflammatory bowel disease, asthma, cancer. The strongest evidence of the beneficial effects of omega-3 fatty acids were obtained in the case of heart diseases.

Table 2

Plant sources of omega-3 fatty acids

Food	Amount	Omega-3 fatty acid (g/serving)	Fiber (g/serving)	Calories/Serving
Flax oil	1 tbs*	7.249	n/a	120
Ground flaxseed	1 tbs	1.597	1.9	37
English walnuts	1 tbs	1.29	0.9	93
Soy oil	1 tbs	0.94	n/a	120
Canola oil	1 tbs	0.862	n/a	120
Tofu, raw, firm	½ cup	0.733	2.9	183
Green soybeans, cooked	½ cup	0.319	3.8	127
Navy beans, cooked	1 cup	0.213	19.1	255
Wheat germ	¼ cup	0.208	3.8	104
Avocado raw	1 cup	0.182	9.8	234
Black walnuts	1 tbs	0.155	0.5	48
Kidney beans, canned	1 cup	0.125	19.1	210
Baked beans, canned	1 cup	0.104	10.4	239

* tbs = tablespoon

Sources: www.nal.usda.gov/fnic/foodcomp/search, www.nutritiondata.com, U.S. Food and Drug Administration.

There are several mechanisms potentially responsible for the effect of omega-3. EPA and DHA, like other fatty acids, integrate themselves into the cell membrane, replacing unsaturated fatty acids. Once incorporated in the membrane, they modulate cellular function (Harris 2005). The omega-3 fatty acids decrease the level of intracellular calcium by blocking the calcium release channels of the sarcoplasmic reticulum, by remodeling the L-type calcium current or by inhibition of Na⁺ channels. This shortens the action potential of the myocytes, directly altering the automaticity or responsiveness of the sinus node, which can reduce the incidence of arrhythmias (Kang et al 2000; Mozaffarian et al 2005; Den Ruijter et al 2008).

Sudden cardiac death is one of the most common first manifestations of coronary heart disease. It is responsible for nearly half of all mortality caused by cardiovascular disorders in the Western world (Zipes et al 1998) Investigators from The Study on Omega-3 Fatty acids and ventricular Arrhythmia (SOFA) studied the effect of omega-3 fatty acids on patients with implantable cardioverter-defibrillators and found that the intake of fish oils reduced the risk of sudden death by 36%. Compared to the rate of death in the placebo group, this value was too small to prove that omega-3 fatty acids have a strong protective effect against ventricular arrhythmia in patients with implantable cardioverter-defibrillators (Brouwer et al 2006). Another trial, GISSI-Prevenzione (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico) found that a diet rich in omega-3 fatty acids is linked to a 14% reduction in death, non-fatal myocardial infarction, and stroke and to a 20% decrease in cardiovascular death (GISSI-Prevenzione 1999). Results of Zutphen study showed that long-term fish consumption was inversely correlated (borderline significant) with (sudden) coronary heart disease death, however, the strength of the correlation decreased with age (Streppel et al 2008).

The acute administration of EPA and DHA determined the reduction of ventricular tachycardias in patients with implanted defibrillator (Schrepf et al 2004). Also, in these patients, omega-3 acids prolonged the time to the first major arrhythmic episode

(ventricular tachycardia or fibrillation) (Leaf et al 2005). In patients undergoing coronary bypass grafting, EPA and DHA suppressed the onset of new atrial fibrillation (Calo et al 2005).

There are studies that failed to demonstrate the beneficial effect of omega-3 acids in reducing the cardiovascular death (the Diet and Reinfarction Trial II) (Burr et al 2003). A Cochrane meta-analysis concluded that "there is not enough evidence to say that people should stop taking rich sources of omega-3 fats, but further high quality trials are needed to confirm the previously suggested protective effect of omega-3 fats for those at increased cardiovascular risk" (Hopper et al 2004).

Heart rate variability is a measure of cardiac electrophysiology that independently predicts sudden death in patients who suffer from cardiovascular diseases and reflects autonomic regulation related to respiratory, baroreflex, and circadian fluctuations and the underlying cardiac responses to this regulation (Kleiger 2005). One trial found that a greater consumption of tuna or other fish was associated with better values of heart rate variability indicators in older people (>65 years), independently from other cardiac risk factors (Mozaffarian et al 2008). This finding is very important because the prevalence of cardiovascular disease is much greater in the elderly.

Several studies proved that omega-3 acids reduce the heart rate and reestablish faster the heart rate after exercises (O'Keefe et al 2006). A meta-analysis, performed in 2005, showed that the reduction of heart rate was linked to a longer period of omega-3 intake (> 12 weeks). This may be explained by the time needed by EPA and DHA to incorporate into the cells and to exert their effects. Heart rate was reduced in people with a higher baseline heart rate. This finding shows that fish oils have greater effect in people with "higher intrinsic sinus node automaticity, greater sympathetic tone, lower vagal tone, or lower ventricular efficiency" (Mozaffarian et al 2005).

Omega-3 fatty acids produce a drastic reduction in fasting and postprandial serum triacylglycerols and free fatty acids, by enrichment in platelet phospholipids and by reducing the production of very low density cholesterol in the liver ["suppression of lipogenic genes and the induction of genes involved in fatty acid oxidation" (Barett et al 2003)]. Omega-3 acids have a positive effect on the increased lipolytic activity of lipoprotein lipase in extrahepatic tissues. They also induce changes in cellular fatty partitioning, initializing the oxidation of the fat tissue and the reduction of the triacylglycerol synthesis. These changes determine a diminution of ectopic fat deposits and organ lipotoxicity (Yvon et al 2006). Several studies revealed that the supplementation of diet with fish oil reduces the level of seric triglycerides.

Fish oils lower blood pressure in humans, possibly by reducing systemic vascular resistance. The effect is small, dose-dependent and the extent is dependent on the degree of hypertension (Kris-Etherton et al 2002). Studies showed that higher proportions of DHA, found in erythrocyte membrane, were associated with improved endothelial function, especially in smokers (Leeson et al 2002). Other studies reported improvements in arterial compliance, attenuation of the expression of cellular adhesion by vascular endothelium. A meta-regression analysis by Geleijnse in 2002 concludes that high intake of fish oil may lower blood pressure, especially in older and hypertensive subjects (Geleijnse et al 2002). Another study showed that treatment with omega-3 fatty acids may reduce the continuous rise in blood pressure after heart transplant (Holm et al 2001).

Major epidemiologic studies proved the cardioprotective effect of EPA, DHA and fish intake on cardiovascular risk in healthy subjects: Nurses' Health Study, the Physicians' Health Study, the Cardiovascular Health Study, the Chicago Western Electric Study, an ecologic study by Zhang et al, the Japan Public Health Center-Based Study Cohort I. Some interventional trials supported the cardioprotective effect of fish oils: the Diet and Reinfarction Trial, the Japan EPA Lipid Intervention Study, GISSI-Prevenzione (Hu et al 2002; Albert et al 1998; Lemaitre et al 2003; Daviglius et al 1997; Streppel et al 2008; Iso et al 2006).

Besides the beneficial effect, a diet rich in fish oils can have negative repercussions. One of the most important side effects is the ingestion of methylmercury, found especially in predator fishes like shark, swordfish, marlin, large species of tuna, mackerel

king. Methylmercury crosses the blood-brain barrier and the placenta (fetal risk), and can cause cardiovascular diseases or neurological damage. Many agencies, like Food and Drug Administration, European Union Health and Consumer Protection Directorate-General and the World Health Organization issued guidelines to limit the methylmercury exposure. Pregnant women, nursing mothers and young children should avoid fish with high levels of methylmercury, should limit their intake of fish with moderate levels of methylmercury, and should consume fish with low levels of methylmercury no more than twice a week.

One other important problem is that large-scale fishing can have ruinous effects on marine ecosystems and their fish populations. Therefore is necessary to weight the benefits and risk of eating fish, to find alternative sources of omega-3 fatty acids, although superior plants and algae do not have the same effect as fish oils (Brunner et al 2008).

The American Heart Association recommends that: "patients without documented coronary heart disease (CHD) eat a variety of (preferably fatty) fish at least twice a week (include oils and foods rich in alpha-linolenic acid: flaxseed, canola and soybean oils; flaxseed and walnuts). Patients with documented CHD should consume about 1 g of EPA+DHA per day, preferably from fatty fish. EPA+DHA in capsule form could be considered in consultation with the physician. Patients who need to lower triglycerides should consume 2 to 4 grams of EPA+DHA per day provided as capsules under a physician's care." (Kris-Etherton et al 2002).

The European Society of Cardiology recommends that patients with stable angina without high risk factors should not receive omega-3 fatty acids supplementation, but they should consume fish at least once a week (Fox et al 2006). The guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death recommends n-3 polyunsaturated fatty acid supplementation and underlying coronary heart disease (Zipes et al 2006). The guideline for prevention of cardiovascular disease concludes that omega-3 fatty acids showed protective effects on fatal events in patients who had suffered a previous myocardial infarction (Graham et al 2007).

Conclusion. Omega-3 fatty acids are a valuable mean of treating and preventing cardiovascular diseases. However, larger and better designed studies are needed to clarify some aspects of omega-3 acids protective effects.

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