European Review for Medical and Pharmacological Sciences 2015; 19: 441-445

Omega-3 fatty acids and cardiovascular disease

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Abstract. – Cardioceuticals are nutritional supplements that contain all the essential nutrients including vitamins, minerals, omega-3-fatty acids and other antioxidants like a-lipoic acid and coenzyme Q10 in the right proportion that provide all round protection tothe heart by reducing the most common risks associated with the cardiovascular disease including high low-density lipoprotein cholesterol and triglyceride levels and factors that contribute to coagulation of blood. Omega-3 fatty acids have been shown to significantly reduce the risk for sudden death caused by cardiac arrhythmias and all-cause mortality in patients with known coronary heart disease. Omega-3 fatty acids are also used to treat hyperlipidemia and hypertension. There are no significant drug interactions with omega-3 fatty acids. The American Heart Association recommends consumption of two servings of fish per week for persons with no history of coronary heart disease and at least one serving of fish daily for those with known-coronary heart disease. Approximately 1 g/day of eicosapentaenoic acid plus docosahexaenoic acid is recommended for cardio protection. Higher dosages of omega-3 fatty acids are required to reduce elevated triglyceride levels (2-4 g/day). Modest decreases in blood pressure occur with significantly higher dosages of omega-3 fatty acids.

Key Words:
Cardioceuticals, Omega-3 fatty acids, Cardioprotection, Eicosapentaenoic acid, Docosahexaenoic acid.

Introduction

Cardioceuticals are nutritional supplements which nourish and protect the heart. While vitamins benefit the heart because of their antioxidant property, they do not provide overall cardioprotection, it is the cardioceuticals which act by providing overall protection. This is achieved by increasing oxygen supply, protection of artery walls and prevention of clots, antioxidation, maintaining healthy rhythm of the heart and lowering of cholesterol.

Some of the important risk factors that need to be addressed by a cardioceutical include low-density lipoprotein (LDL) cholesterol levels, oxidative damage and effects of reactive oxygen species. They reduce the risk of sudden death, heart attack, prevent abnormal heart rhythms and strokes in cardiovascular disease patients. The build-up of atherosclerotic plaque scan also be prevented by the use of these nutritional supplements. An ideal cardioceutical should contain all the essential nutrients including vitamins, minerals, omega-3-fatty acids and other antioxidants like a-lipoic acid (ALA) and coenzyme Q10 in the right proportion that will provide all round protection to the heart by reducing the most common risks associated with the cardiovascular disease including high LDL cholesterol and triglyceride levels and factors that contribute to omega-3 fatty acids and cardiovascular disease coagulation of blood. The focus of this article is on role-of omega-3 fatty acids in cardiac protection.

Omega-3 fatty Acids and Cardioprotection

Over the past 20 years, there has been a marked increase in the scientific scrutiny of and public interest in omega-3 and omega-6 fatty acids and their impact on personal health. Omega-3 fatty acids possess anti-inflammatory, antiarrhythmic and antithrombotic properties; omega-6 fatty acids are proinflammatory and prothrombotic. Increased consumption of vegetable oils high in omega-6 fatty acids (such as corn, safflower, sunflower and cotton seed oils) and meats from animals that were fed grains high in omega-6 fatty acids has drastically shifted the dietary ratio of omega-6 to omega-3 fatty acids from an estimated 1:1 in the early human diet to approximately 10:1 in the typical modern American diet[1].

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Omega-3 and omega-6 fatty acids are essential because they are not synthesized by the body and must be obtained through diet or supplementation. Through an inefficient enzymatic process of desaturation (the rate of conversion is < 1%), ALA produces eicosapentaenoic acid (EPA) (20 carbons) and docosahexaenoic acid (DHA) (22 carbons), precursors to a group of eicosanoids (prostaglandins, thromboxanes and leukotrienes) that are anti-inflammatory, antithrombotic, antiarrhythmic and vasodilatory. The longer chain fatty acid derivative of linoleic acid is arachidonic acid (20 carbons), which is a precursor to a different group of eicosanoids that are proinflammatory and prothrombic. ALA and linoleic acid use and compete for the same enzymes in the production of their longer chain fatty acids, EPA and arachidonic acid. The ingestion of fish and fish oil provides EPA and DHA directly, therefore avoiding the competition for enzymes to convert ALA to EPA[1].

Mechanism of Cardioprotection

Omega-3 fatty acids have been shown to be cardioprotective due to multiple mechanisms.

Antiarrhythmic Effect

It is thought that omega-3 fatty acids stabilize the electrical activity of cardiac myocytes by inhibiting sarcolemmal ion channels, resulting in a prolonged relative refractory period[2].

Antithrombotic Properties

The omega-3 fatty acids demonstrate significant thrombotic properties. EPA has been shown to inhibit the synthesis of thromboxane A2, a prostaglandin that causes platelet aggregation and vasoconstriction[3].

Ingestion of EPA has also been shown to reduce platelet adhesion and reactivity, which manifests itself as increased bleeding time and decreased adhesion of platelets to glass beads[4]. Reductions in fibrinogen and increases in tissue plasminogen activator are some of the other antithrombotic effects which have been reported[5,7].

Endothelial Function

Endothelial function is also favorably affected by omega-3 fatty acids because the vasodilatory effect of nitrous oxide is enhanced by EPA. Treating humans with fish oil has been shown to decrease oxygen-derived free radical production in neutrophils[6]. It has been suggested that this reduction in free radicals increases the bioavailability of nitrous oxide. Studies[8] using ultrasonic tracking of brachial artery flow-mediated vasodilation have demonstrated improved large artery endothelium-dependent dilation in patients treated with fish oil. Endothelial function can also be improved by reducing the endothelial expression of vascular cell adhesion molecules, thus resulting in a reduction in leukocyte binding to the endothelium[9].

Inhibition of Atherosclerotic Plaque Formation

Ingestion of EPA and DHA also has been shown in animal studies to inhibit atherosclerotic plaque formation. Two important cells in the development of an atherosclerotic plaque are smooth muscle cells and macrophages. Platelet-derived growth factor is a key chemoattractant and mitogen for smooth muscle cells and macrophages. Platelet-derived growth factor production and messenger RNA synthesis are decreased by the ingestion omega-3 fatty acids[10].

Lipid Metabolism

The effect on lipid metabolism is predominantly antiatherogenic. Consuming fish oil (a rich source of EPA) has been shown to lower total cholesterol and triglyceride concentrations by inhibiting very LDL and triglyceride synthesis in the liver[10]. Large doses of fish oil have been shown to have profound effects in reducing triglyceride levels in hypertriglyceridemic patients. Apolipoprotein B production is also reduced by fish oil consumption compared with vegetable oils not containing omega-3 polyunsaturated fatty acids[11,12].

Pre-treatment with omega-3 fatty acids also markedly reduces postprandial lipemia, which typically occurs after consumption of a fatty meal, and postprandial lipoproteins are atherogenic. Postprandial lipemia is also thrombogenic because it increases levels of activated factor VII, a procoagulant. Ingesting olive oil results in the same degree of increase in factor VII as ingesting butter, whereas consuming fish oil prevents this postprandial increase[13]. Omega-3 fatty acids have been shown to result in a favorable change in high densitylipoprotein (HDL) cholesterol metabolism.

It seems that omega-3 fatty acids cause an increase in the large cholesterol-rich HDL2 subtype while decreasing the smaller triglycerol-enriched HDL3 subtype[14,15]; HDL2 is considered to be the most antiatherogenic HDL subtype.

Evidence from Clinical Trials

In the past three years, at least three major meta-analyses of omega-3 fatty acids and their relationship to cardiovascular morbidity and mortality were published[16-18] which concluded that fish oils supplementation is associated with a decrease of the risk of cardiovascular events and cardiovascular disease death rates. In terms of cardiovascular efficacy and safety of omega-3 fatty acids, there are three most important clinical studies: The Diet and Reinfarction Trial (DART) study, the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI) Prevenzione and GISSI-HF trials and the Japan EPALipid Intervention Study (JELIS) study.

DART Study

In the DART, 2033 men after myocardial infarction were followed for two years. These were randomly assigned to a group instructed to increase fish intake to achieve daily consumption of EPA and DHA of approximately 900 mg or to a control group that received no specific information. The intervention group experienced 29% reduction in all-cause mortality and the incidence of reinfarction was reduced by 32%[19].

The JELIS[20], the second study that usually belongs to the core evidence in any meta-analysis is the JELIS. It was a very large trial following 18,645 patients with hyperlipidemia (> 3.500 of which had a history of avascular event). The study subjects were randomly assigned to either statin alone or a combination of statin and 1.8 g of EPA daily. After five years, the combination treatment was associated with a significant reduction of the primary composite endpoint comprising death, revascularization, myocardial infarction and unstable angina by 19% compared to the statin alone group. A post-hoc analysis of the secondary prevention subgroup revealed similar benefit of the statin +EPA combination of cardiovascular outcomes in this subgroup in which relative risk was reduced by 23%[21]. The greatest relative risk reduction of 53% in primary prevention was experienced in patients with increased triglyceride and decreased HDL cholesterol levels[22].

GISSI-Prevenzione Study[23]

The third study providing a substantial part of the data in the meta-analyses is the GISSI-Prevenzione study. Eleven thousand three hundred twenty-three survivors of myocardial infarction were randomized to 850 mg of DHA/EPA daily or usual care. Treatment significantly reduced risk of death from any cause by 28% after only four months, being driven mainly by the lowering of sudden cardiac death risk by 45%. The differences remained significant for the whole 3.5-year duration of the study. Effects of omega-3 fatty acids were studied by the same group in a population of heart failure patients[24]. Three thousand four hundred ninety-four patients with heart failure were randomized to 850 mg of omega-3 fatty acids daily and 3,481 received matching-placebo. DHA/EPA administration reduced the risk of death from any cause by 9% ($p = 0.041$) and hospitalization for cardiovascular reasons by 8% ($p = 0.009$), which means 56 patients needed to be treated for 3.9 years to prevent one death.

Recommendations

Guidelines of various expert societies including American Heart Association[25], American Diabetes Association[26] as well as the joint guidelines on cardiovascular prevention of nine European societies[27] are in conformity with most meta-analyses and reports from well-conducted clinical trials. They concur that the evidence is particularly well-proven in secondary prevention and (although less robust) it is reliable in primary prevention setting, too.

For the primary prevention of cardiovascular events it is currently recommended to maintain the daily intake of DHA and EPA in the range of 300-600 mg. In secondary prevention higher dose of 900-1.200 mg aday is well-supported by the evidence. For the reasons of triglyceride lowering even higher dose between 3.000 and 4.000 mg of DHA and EPA is suggested. The recommended intake of omega-3 fatty acids can be achieved by increased oily fish consumption; however, for the purpose of triglyceride lowering dietary supplements of concentrated EPA/DHA are usually necessary. A standardized capsulated concentrate of EPA and DHA as a prescription drug is also available in the USA and some European countries[28,29].

Future Directions

In the future, the recommendation is that the dose should be according to the actual need of a particular patient based on the measurement of plasma concentration of omega-3 fatty acids. As reviewed by Albert et al[30] concentrations of omega-3 fatty acids in plasma are strong predictors of sudden cardiac death. Therefore, Harris et al[31] hase proposed a new marker of cardiovascu-

lar risk – an omega-3 index[31]. This index reflects the proportion of omega-3 fatty acids in the membrane of red blood cells. Omega-3 index exceeding 8% is associated with the lowest risk of cardiovascular events while levels < 4% are typically found in coronary artery disease patients[30]. Thus, omega-3 index may help identify those who would benefit most from omega-3 fatty acids supplementation.

Conclusions

Therapy with low-dose omega-3 fatty acids significantly reduces the incidence of sudden death caused by cardiac arrhythmias and all-cause mortality in patients with known coronary heart disease. Results of individual clinical trials as well as meta-analyses of omega-3 fatty acids impact on cardiovascular outcomes provide enough evidence to encourage intake of EPA/DHA daily in primary and secondary prevention[33] of cardiovascular disease, respectively[31]. The target EPA + DHA consumption should be at least 500 mg/day for individuals without underlying overt cardiovascular disease and at least 800-1.000 mg/day for individuals with known coronary heart disease and heart failure.

Further studies are needed to determine optimal dosing and the relative ratio of DHA and EPA omega-3 polyunsatured fatty acid that provides maximal cardioprotection in those at risk of cardiovascular disease as well in the treatment of atherosclerotic, arrhythmic and primary myocardial disorders[34]. In the future, more personalized recommendation based on assessment of individual omega-3 fatty acids needs (using e.g. omega-3 red blood cell index) would be possible.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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