IMPORTANT BIOACTIVE PROPERTIES OF OMEGA-3 FATTY ACIDS

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ABSTRACT

Good health has been linked with healthy diet. N-3 fatty acids are required for proper functioning of many physiological systems. There is a large body of evidence documenting the effects of polyunsaturated fatty acids with the first double bond at the third position from methyl-terminal on health benefits. Scientific evidence is accumulating to substantiate the role omega-3 fatty acids play in conditions such as cardiovascular disease, certain cancers and other diseases. The availability of n-3 fatty acids to various tissues is of major importance to health and depends on dietary intake for both normal development and in the prevention and management of chronic diseases. In this review we will summarize the biological properties of omega-3 fatty acids.

- Keywords: omega-3 fatty acids, polyunsaturated fatty acid, biological properties, health -

INTRODUCTION

Long-chain polyunsaturated fatty acid (PUFA) with the first double bond at the third position from the methyl-terminal (so called omega-3 fatty acids or n-3 fatty acids) can be found in plants and fish. N-3 fatty acids refer to a group of three fats called alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Because these essential fatty acids cannot be synthesized in the human body, they must be derived from dietary sources. They are required for the structure of cell membranes and, because they are unsaturated, they help keep membranes flexible. The peculiar properties of the DHA molecule make it a critical component of nerve and retinal cells. Flaxseed, hemp, canola and walnuts are generally rich sources of the ALA. Fish provide varying amounts of n-3 fatty acids in the form of DHA and EPA. The n-3 PUFA are obtained predominately from fish, seafood, meat and eggs (MEYER *et al.*, 2003) and in recent years from enriched food products such as bread, milk and margarine. The role played by essential fatty acids in the human body has been the subject of volumes of international research in recent years. The results indicate that n-3 fatty acids may be of value in the treatment of various medical conditions (UAUY and VALENZUELA, 2000). Research has been carried out in animal models, tissue cultures and human beings. A present study was to produce pork with enhanced nutritive value for humans, in terms of fatty acid profile. When fish oil was included in the diet, higher levels of EPA, DPA and DHA were measured in the subcutaneous fat (MOREL *et al.*, 2013). The positive effects of essential fatty acids are attributed to their ability to reduce inflammation (SIMOPOULOS, 2002). Many studies show that fish oil with high content of n-3 polyunsaturated fatty acids (PUFAs) plays an important role in human health and disease. But the effects of fish oil with high content of PUFAs on gut microbiota, which are also known play a significant role in several human diseases, is not clear. YU *et al.* (2014) evaluated the effects of fish oil with high content of n-3 PUFAs on gut microbiota. They found that fish oil treatment resulted in a decrease in *Helicobacter, Uncultured bacterium clone WD2_aaf07d12* (GenBank: EU511712.1), *Clostridiales bacterium, Sphingomonadales bacterium and Pseudomonas species Firmicutes*, and several uncultured bacteria. Fish oil with a high content of n-3 PUFAs are capable of producing significant changes in the gut microbiota that may, at least in part, explain the health benefits or injury induced by fish oil use.

In recent years, the number of studies describing the health-promoting benefits of n-3 fatty acids has increased. Some of the reported activities attributed to the n-3 fatty acids include improving serum cholesterol profiles, stabilizing arrhythmias, reducing inflammation, improving insulin sensitivity in patients with Type 2 diabetes, and enhancing the immune response. In this paper, we will discuss diverse effects of an essential component of a healthy diet, long chain n-3 PUFA. Because modern diets are relatively deficient in this special type of fat, there is a great potential for improving many aspects of health by adding it to the diet.

Cardiovascular disease

Cardiovascular disease (CVD) includes all diseases of the blood vessels and circulatory system such as coronary heart disease (CHD), ischemic heart disease (IHD), myocardial infarction (MI) and stroke. CVD is the leading cause of death in Canada and the United States. Since the original epidemiological observations of low CVD mortality in populations with high consumption of fish there has been continuous interest of scientific communities in the possibility of lowering CVD risk by n-3 fatty acids. Both EPA and DHA play a role in modification of lipid and lipoprotein metabolism. N-3 fatty acids have synergistic and additive effects on plasma lipids when co-administered with statins (DAVIDSON *et al.*, 2007). Increased triglyceride levels are seen among individuals with HIV who receive antiretroviral therapy. A study reported the results of a research that examined the effects of a controlled dietary study supplemented with 4 g of fish oil daily to reduce triglyceride levels in HIV (CAPILI and ANASTASI, 2013). Another practical implication of such studies is the proven safety of n-3 fatty acids add on therapy to statins. Both DHA and EPA have profound effect on platelet function. Not only membrane stabilizing effect but also competition of n-3 fatty acids for cyklooxygenase activity with arachidonic acid, which lowers production of platelet activating eicosanoids play an important role (LARSON *et al.*, 2008). In a study in diabetic patients Woodman and co-workers demonstrated administration of highly purified EPA/DHA was associated with a decrease in platelet aggregability by 30 % (WOODMAN *et al.*, 2003). The platelet effects seem to be mediated mostly by EPA (DIN *et al.*, 2008). OLIVEIRA *et al.*(2014) suggested that fish oil upregulate the expression of the cholesteryl ester transfer protein (cetp) gene.

Another possibly cardioprotective action of n-3 fatty acids can be modulation of immune response and anti-inflammatory properties. As demonstrated *in vitro*, DHA lowers cytoadhesive molecules expression on endothelial cells and monocytes (MORI and BEILIN, 2004). Similarly, levels of interleukin 6, interleukin 1β and tissue necrosis factor α decrease after EPA/DHA administration (BHATNAGAR and DURRINGTON, 2003). Consumption of n-3 fatty acids of 8 g/d was associated with a significant reduction of inflammatory marker levels in patients with severe heart failure (MEHRA *et al.*, 2006).

Some studies have shown that n-3 fatty acids may increase the susceptibility of LDL to oxidation (SORENSEN *et al.*, 1998), whereas others have not (HIGDON *et al.*, 2001). It therefore remains to be established whether LDL oxidative status in vivo is affected by omega-3 fatty acids and, if so, whether this has any adverse clinical implications

Cancer

Cancer is another disease that has generated great interest in evaluating the usefulness of n-3 fatty acids. Cancer and its treatments are associated with significant long-term side effects such as cachexia, cognitive impairment, distress, pain and fatigue that all warrant supportive care. Many experimental studies have shown the role played by n-3 fatty acids in suppressing the development of most cancer processes, including breast, colon, prostate, liver and pancreatic cancers (SIMOPOULOS, 2009). In addition, there is evidence that EPA and DHA exert a potent antiangiogenic effect, inhibiting the production of some of the main angiogenic mediators (SPENCER *et al.*, 2009). This explains the great interest in establishing fatty acid ingestion in adequate proportions.

EPA has been suggested to play a protective role in hormone-related cancers, particularly breast and prostate cancers. In animal experiments, EPA and DHA have consistently inhibited the proliferation of malignant breast and prostate cancers; however, epidemiological studies examining the role of n-3 fatty acids in cancer have not been consistent (TERRY *et al.*, 2003). Fish oils can have a benefit in reversing cancer-related cachexia by decreasing the protein degradation in cachectic muscle (TISDALE, 2003), suggesting that there may be a potential place for n-3 fatty acids in cancer therapy as well as in prevention. XUE *et al.* (2014) suggested that DHA exerted its anticancer activity through down-regulation of Wnt/β-catenin signaling. Thus, it should call for further studies to assess the effectiveness of fish oil as a dietary supplement in the prevention and treatment of breast cancer.

In the last decade, many clinical trials examining the effects of n-3 fatty acids supplementation on cancer cachexia have been conducted (RIES *et al.*, 2012). Some randomized controlled trials confirmed these results, especially at dosages of 1.5–2 g EPA-enriched enteral liquid formula administrated for at least 8 weeks in gastrointestinal or pancreatic cancers (RYAN *et al.*, 2009). Clinical studies are emerging to support providing long chain n-3 fatty acids to prevent muscle loss, minimize side effects and improve chemotherapy response in patients with cancer (MURPHY et al., 2013). A research suggests that marine n-3 fatty acid may increase appetite (SIGNE *et al.*, 2013). This finding would be potentially beneficial for patients with compromised nutritional status.

Bone

The n-3 and n-6 polyunsaturated fatty acids are the immediate precursors to a number of important mediators of immunity, inflammation and bone function, with products of n-6 generally thought to promote inflammation and favour bone resorption. Western diets generally provide a 10 to 20-fold deficit in n-3 PUFAs compared with n-6, and this is thought to have contributed to the marked rise in incidence of disorders of modern human societies, such as heart disease and osteoporosis. Osteoporosis is a disease in which bone mass is low and the risk of bone fractures is high. Regarding bone diseases, studies in animals have shown that the ingestion of n-3 fatty acids could influence bone formation and resorption (POULSEN, 2007). ALA may help prevent bone loss and osteoporosis by blocking the production of tumor necrosis factor α, which promotes bone resorption and inhibits bone formation (BOYCE *et al.*, 2005). When bone metabolism was measured in the volunteers, the high-ALA diet reduced bone resorption without reducing bone formation (ZHAO *et al.*, 2007). The decrease in bone resorption may have been due to a decrease in the dietary n-6/n-3 ratio as a result of the high-ALA diet. TARLTON *et al.* (2013) found that there was a significant 40–60% reduction in keel bone breakage rate, and a corresponding reduction in breakage severity in the n-3 supplemented hens. The biomechanical and biochemical evidence suggests that increased bone turnover has enhanced the bone mechanical properties, and that this may suggest potential benefits for human osteoporosis.

However, some studies found no effect of n-3 fatty acids consumption on measures of bone formation and resorption among postmenopausal women (DODIN *et al.*, 2005; BROOKS *et al.*, 2004). These results suggest that the benefit of n-3 fatty acids on bone metabolism is not sufficient to overcome the bone remodeling that occurs during menopause.

Emotional distress

Most newly diagnosed and recurrent cancer patients presented with a significant level of mental distress. Commonly, distress involves anxiety and depression. A study reported that the antidepressant protective role of n-3 fatty acids might be exerted through production of eicosanoids that are able to reduce the excessive pro-inflammatory cytokine production in depressed patients (KIECOLT-GLASER *et al.*, 2007). Animal studies in which rats were fed an n-3 fatty acids rich diet indicated a better habituation to chronic restraint stress as they showed less stress-induced weight loss, compared to both control and n-3 deficient rats (HENNEBELLE *et al.*, 2012). Several clinical trials addressing non-cancer populations have also suggested beneficial effects of n-3 fatty acids on anxiety and depression (LUCAS *et al.*, 2009; ARBABI *et al.*, 2014). However, no trials were found exploring the potential benefits of plant-derived EPA. Similar positive results were found by TAJALIZADEKHOOB *et al.* (2011) in elderly patients. Although the potential benefits of n-3 fatty acids on emotional distress per se have not been examined as a primary endpoint in cancer patients, one trial did study depressive symptoms in lung cancer patients. The trial reported an inverse association between n-3 fatty acids intake, as well as serum n-3 fatty acids and minor depression (KOBAYAKAWA *et al.*, 2005). Though controversy exists as to whether EPA, DHA or both are responsible for the efficacy of n-3 fatty acids in depression, results from a randomized controlled trials suggested EPA to be a more effective fatty acid component in the treatment of mild to moderate depression (MOZAFFARI-KHOSRAVI *et al.*, 2013).

There is also evidence that the pathophysiology of major depression is influenced by changes in fatty acid intake. In 2009, DINAN *et al.* evaluated the levels of arachidonic acid, IL-6 and TNF α in depressed responders and non-responders to antidepressive treatment. There were significant differences in the EPA and arachidonic acid ratio between controls and responders versus non-responders. One research reinforces these observations in major depression and bipolar disorder, and low DHA levels may even predict suicidal behaviour (MCNAMARA *et al.*, 2008). It has been shown that DHA content in brain tissue is decreased in patients with neuronal alterations, as in Alzheimer's disease.

Obesity

Obesity, a chronic low-grade inflammatory condition, is considered to be a metabolic disorder, whose prevalence is increasing dramatically in most developed countries over the last 20 years. Obesity is associated with an increased risk of CVD, type 2 diabetes and a number of cancers. One study suggests that at baseline men with high fish consumption were less likely to be overweight, however no data about association of n-3 fatty acids intake and changes in BMI (body mass index) were provided in this 12-year follow-up cohort (HE *et al.*, 2002). The effects of a combination of n-3 fatty acids and a dietary energy restriction in obese volunteers were also examined. PARRA *et al.* (2008) showed that satiety was increased after consumption of the n-3 fatty acids-enriched meals. Researches have demonstrated that diabetes induces learning and memory deficits (JIA *et al.*, 2014). The results suggested that the principle mechanisms involved in the antidiabetic and neuroprotective effect of fish oil were its antioxidant, anti-inflammatory and anti-apoptosis potential, supporting a potential role for fish oil as an adjuvant therapy for the prevention and treatment of diabetic complications. Dietary fish oil showed better tissue preservation that was supported by histopathological observations (JANGALE *et al.*, 2013). Thus, the diet proved to be beneficial in preventing tissue injury and alleviating diabetic insults in the livers of diabetic rats. A recent research explored insulin signaling in the newborn rat heart. A diet rich in fish oil improves cardiac Akt-related signaling in the offspring of diabetic rats (NASU-KAWAHARADA *et al.*, 2013).

HILL *et al.* (2007) found that exercise and n-3 fatty acids supplementation resulted in a significant reduction of body fat. However, MUNRO and GARG (2012) described that dietary supplementation with n-3 fatty acids did not promote additional weight loss when combined with a very-low-energy diet for 4 weeks. The most possible cause for the disparities in these results may be related to phenotypical characteristics of the subjects included in the study. Indeed, mechanisms underlying this differential response in body weight in obese humans remain a challenging point still to be addressed in future. It should be stated that the effects of n-3 fatty acids on fat mass and weight regulation might be difficult to address due to important differences in how the studies were designed as well as the inclusion criteria and source for n-3 fatty acids supplementation. Therefore, effectiveness of the n-3 fatty acids supplementation might be related to dietary and exercise patterns and gender aspects might also be relevant.

However, the effects of these fatty acids on insulin sensitivity remain controversial (KABIR *et al.*, 2007; NAVAS-CARRETERO *et al.*, 2009; HIRABARA *et aal.*, 2013), the fact is that insulin resistance is usually linked to other pathological conditions such as hypertrigliceridemia, overweight and cardiovascular diseases and might be difficult to study on itself. Thus, further studies are needed to evaluate this aspect of n-3 fatty acids in insulinemia management.

Nutritional recommendations for the consumption of n-3 fatty acids

As we have seen, there are a number of pathologies in which the n-3 fatty acids play an important role, thus reflecting the importance of ensuring their adequate dietary intake. Recommendations for dietary intakes of n-3 PUFA vary considerably from the consumption of two fish meals a week to EPA plus DHA intakes of 500 mg/d (KRIS-ETHERTON *et al.*, 2002) and the Japanese recommend consumption of n-3 PUFA of 1.6 g/d (SUGANO, 1996). An approximate estimation of the consumption of n-3 fatty acids in Europe is 0.1-0.5 g/d. These datas are high in comparison to the estimated intake of DHA and EPA in the United States (0.1-0.2 g/d), but low in comparison with the data corresponding to Japan (up to 2 g/d), where fish is one of the most commonly consumed foods (CARRERO *et al.*, 2005). In Spain, a study carried out by the Ministry of Agriculture, Fisheries and Food, showed that the fact that the Spanish population consumes levels of n-3 close to the recommended level (1.52 g/d). However, the percentage of energy contributed by EPA+DHA with respect to total energy in the diet was lower than the recommended value (0.5%). ALA, the precursor of n-3 fatty acids, can be converted to long-chain n-3 PUFA. The minimum intake of n-3 PUFA needed for beneficial effects depends on the intake of other fatty acids. Dietary amounts of linoleic acid (LA) as well as the ratio of LA to ALA appear to be important for the metabolism of ALA to n-3 PUFA. Indu and GHAFOORUNISSA (1992) showed that a ratio of 4 is appropriate for conversion. This ratio is also consistent with a study by DE LORGERIL *et al.* (1994).

On comparing the recommendations for n-3 consumption of the different organizations and the existing consumption data, the results show that the consumption of n-3 fatty acids is generally low. The recommendations of the American Heart Association (AHA) are that adults should consume fish at least twice a week. Likewise, patients with coronary disease should consume 1 g of EPA+DHA daily; while patients with hypertriglyceridemia should consume 2-4 g/d of EPA+DHA (BAGGA *et al.*, 2002). Taking the above into account, the recommended amounts must be adjusted according to the specific needs for the different diseases, and other important dietary factors. In a sense, an increase in n-3 fatty acids in the diet may be regarded as important. From the above we can deduce that a considerable increase in fish consumption is required.

Maternal levels of n-3 fatty acids during pregnancy determine the levels present in the developing infant. The n-3 fatty acids DHA is critical in supporting infant growth and development, and DHA levels in newborns are correlated with birth weight and head circumference. It has been suggested that women and their infants may benefit if the mother is supplemented with DHA during pregnancy. Breast milk contains about 0.5-2.0% ALA and about 0.1-0.4% DHA (INNIS, 2000). ALA constitutes 75-80% of the total n-3 fatty acids in breast milk (SILVA *et al.*, 2005), supporting a role for ALA in the growth and development of infants.

The diets of Western countries have contained increasingly larger amounts of LA. Essential fatty acids also have antibacterial actions and are found in breast milk (Das, 2006). Indeed, breast milk is rich in LA and contains more of ALA than of any other omega-3 fatty acid (SILVA *et al.*, 2005).

CONCLUSIONS

Our message is that omega-3 fats can contribute to a longer and healthier life. Most studies indicate that the consumption of n-3 fatty acids should be more than that presently found in the general population, with a view to improving general health and reducing the risk of disease. However, further studies are needed to confirm and consolidate this idea. The future study offers the opportunity to clarify the underlying molecular mechanisms and elucidate the observed differences between different ethnic groups and genders in developing population-specific dietary recommendations.

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