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RESEARCH ARTICLE

Effect of omega 3 fatty acids family in human health

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Abstract

Omega 3 fatty acids family is apart from two parts of essential fatty acids that cannot be human body synthesized which have great importance in maintaining human health. This family divided to a group of fatty acids that starts with alpha-linolenic acid (ALA) (C18: 3n-3) and ends with docosahexaenoic (DHA) (22:6n-3). Flaxseed oil is richest plant source of alpha-linolenic acid, while cold water fish is richest source of eicosapentanoic and docosahexaenoic. This family play important role in maintaining heart health and safety of the arteries. In this review we discuses this type of fatty acids, its divisions, its sources and its significance role in human health.

1. Essential fatty acids as important nutrient for human.

Essential fatty acids (EFA) and their derivatives played the major role in lipid metabolism, platelet functions, immune system, inflammatory response, and epidermal functions, it is important to assure optimal EFA intakes **(Sardesai, 1992)**. Dietary essential fatty acids (EFA), linoleic acid [18: 2(n-6), LA] and alpha-linolenic acid [18:3(n-3), ALA] are converted to long-chain polyunsaturated fatty acids (LCPUFAs) by desaturase and chain-elongation enzyme systems (**Holman, 1998)**. Phospholipids, cholesterols, saturated fatty acids and monounsaturated fatty acids can be synthesized de novo within the human body. Because mammals cannot introduce a double bond beyond the delta-9 position in the fatty acid chain, however, linoleic (n-6) and linolenic acid (n-3) must be ingested in the diet **(Wayne et al., 2000)**. Each of these EFA is in turn the substrate for further desaturation and elongation. The substrates and products comprise twelve essential fatty acids in 2 noninterchangeable series: n-6 [linoleic (18:2n-6); gamma linolenic (18:3n-6); dihomogammalinolenic (DGLA) (20:3n-6); arachidonic (AA) (20:4n-6, and n-3: [alpha linolenic (ALA) (18:3n-3); strearidonic (18:4n-3); eicosatetraenoic (20:4 n-3); eicosapentanoic (EPA) (20:5n-3); docosapentaenoic (22:5n-3); docosahexaenoic (DHA) (22:6n-3)]. The n-3 and n-6 designation indicate that the third or sixth carbon bond respectively from the methyl end of the hydrocarbon chain is unsaturated. The PUFA are classified into omega-3 (or n - 3) and omega-6 (or n - 6) groups. The parent essential fatty acid of omega-3 PUFA is alpha-linolenic acid (ALA; C18:3n - 3), and that of omega-6 group is linoleic acid (LA; C18:2n - 6). The cerebral cell membrane contains high concentrations of PUFA, some of which cannot be synthesized and therefore must be obtained from the diet. The abnormalities in PUFA composition in cell membranes can alter membrane microstructure, which could result in abnormal signal transduction and immunological dysregulation, and possibly can increase the risk of developing depression **Chiu et al., (2003)**. Alpha-linolenic acid, [ALA or 18:3(n-3) or 18:3 omega-3] is one of the two essential fatty acids in humans. The other one is linoleic acid [LA or 18:2(n-6)]. The term essential means that these fatty acids must be supplied in the diet because the body needs them but cannot synthesize them. Humans actually lack the enzymes to introduce double bonds at carbon atoms beyond the carbon-9 in the fatty acid chain **(De Lorgeril, and Salen, 2004)**. EFA are essential for humans and as are not synthesized in the body; have to be obtained in our diet **(Das, 2006)**. LA and ALA are essential PUFA since mammalian cells are unable to synthesize these PUFA from simpler precursors **(Brian, 2007**). LA can be converted via a biosynthetic pathway into longer chain n- 6 PUFA such arachidonic acid (AA) and dihomogammalinolenic acid (DGLA), and ALA into long chain n- 3 PUFA such as eicosapentaeoic acid (EPA) and docosahexaenoic acid (DHA). Dietary LA and ALA are metabolized by the enzymes D6 and D5 desaturases to their respective metabolites. LA, ALA, and oleic acid (OA, n-9 fatty acid) are metabolized by the same set of D6 and D5 desaturases and elongases. As a result, these three series compete with one another for the same set of enzymes, though the enzymes seem to prefer n-3 to n-6 and n-6 over n-9. Hence, under normal physiological conditions the metabolites of n-9 are formed only in trivial amounts in the cells. Thus, presence of significant amounts of 20:3 n-9 indicates EFA (LA and ALA) deficiency. The activities of D6 and D5 desaturases are slow in humans **(Undurti, 2007)**. As a result, the conversion of LA and ALA to their respective metabolites may be inadequate under certain conditions. In such instance, it is necessary to supplement GLA and DGLA (to bypass D6 desaturase) and AA and EPA and DHA (to bypass D6 and D5 desaturases). Generally, supplementation of AA is not necessary since; it can be obtained from the diet. Western diet is rich in n-6 fatty acids compared to n-3 fatty acids (n-6 to n-3 ratio is 10:1), whereas the recommended ratio is 1:1.Saturated fats, cholesterol, trans-fatty acids, alcohol, adrenaline, and glucocorticoids inhibit D6 and D5 desaturases. Zinc, magnesium, calcium, biotin and vitamins B6, B3 and C are co-factors for normal D6 desaturase activity. The balance between arachidonic acid (C20:4 n6) and long-chain (LC) omega-3 PUFA [eicosapentaenoic acid (EPA, 20:5n3) and docosahexaenoic acid (DHA, 22:6n3)] in cells and tissues is known to directly influence prostanoid biosynthesis, which mediates the inflammatory process **(Watkins et al., 2007)**.

2. Omega 3 fatty acids family.

2.1. Alpha-linolenic acid (ALA).

Interest in n-3 fatty acids began some 30 years ago and now culminates in these comprehensive proceedings of the International Conference on Highly Unsaturated Fatty Acids in Nutrition and Disease Prevention, held in Barcelona, November 4-6, 1996. The remarkable concurrence and agreement regarding n-3 fatty acids is evidenced by the several thousand papers extant in the literature **William, (2000)**. Omega-3 fatty acids are polyunsaturated; with their first double bond exactly 3 carbons from the lipophilic end of the molecule. A series of double bonds recur every third carbon atom. The presence of multiple double bonds in the carbon chain produces a more highly folded molecule than more saturated fatty acids. In addition, the melting point of the omega-3 fatty acids is much lower than for more saturated fatty acid, which explains why membranes containing a high content of omega-3 fatty acids may be more 'fluid' at a given body temperature, when compared with membranes comprised of more saturated fatty acids **(Sprecher, 1981)**. The main sources of alpha-linolenic acid for the European population should be canola oil (and canola-oil based margarine if available), nuts (English walnut), ground linseeds and green leafy vegetables such as purslane **(De Lorgeril, and Salen, 2004)**. The amount of ALA in milligrams per gram wet weight of purslane and other commonly eaten leafy vegetables (spinach, buttercrunch lettuce, red leaf lettuce, and mustard greens) were determined by **(Simopoulos, 2004)**. Purslane contains 8.5 mg of fatty acids per gram of wet weight. In contrast, the other plants are relatively low in lipid content: spinach contains 1.7 mg/g, mustard greens 1.1 mg/g, red leaf lettuce 0.7 mg/g, and buttercrunch lettuce 0.6 mg/g. Purslane, with 4 mg of 18:3 n-3/g wet, is a good nonaquatic source of 18:3 n-3. ALA is a plant form of omega-3 fatty acid. The major dietary sources in the human diet are soybean and canola oils. In addition, the amounts in flaxseeds and walnuts and their respective oils are high and when consumed can provide relatively high levels of intake **Ethan et al., (2006)**. ALA found in flaxseed oil (FO) desaturates and elongates in the human body to eicosapentanoic acid (EPA) and docosahexanoic acid (DHA) and by itself may have beneficial effects in health and in control of chronic diseases **Mantzioris et al., (1994**). The omega-3 fatty acids (also known as 'n-3' fatty acids) are a group of naturally occurring lipids, occurring in high concentrations in plants, such as flax seed oil, perilla oil and others **(Cunnane et al., 1995)**. The omega-3 fatty acids are considered 'essential', in that humans must ingest omega-3 fatty acids from their diet, since the omega-3 structure cannot be synthesized in humans **(Stoll et al., 1999)**. Alpha-linolenic acid is the major plant omega-3 fatty acid. Flaxseed oil is the richest natural source of this fatty acid, but alpha-linolenic acid is also present in large amounts in a variety of other plant oils **(Charles and Myers, 2000)**. Increased intake of this fatty acid has been associated with a decrease in blood cholesterol levels and may reduce the risk of heart attacks. The n-3 alpha-linolenic acid was only a precursor of the long-chain fatty acids EPA and DHA **(Lauritzen et al., 2001)**. An alternative source of n- 3 PUFA is alpha-linolenic acid (ALA; 18:3 n-3), which in stable-isotope studies in human was shown to be desaturated and elongated to EPA and DHA **(Pawlosky et al., 2001 and Lee and Lip, 2003)**. This is a major point as ALA, because of its three double bonds, is highly sensitive to oxidation and high intake of ALA must be balanced with high intake of antioxidant to protect it from oxidation **(De Lorgeril, and Salen, 2004**). The n-3 PUFA (ALA) in flaxseed oil have anti inflammatory properties that are mediated by the production of anti-inflammatory eicosanoids **(Cohen et al., 2005**).High intakes of ALA have been reported to result in significant increases in very long chain omega-3 fatty acids in various body compartments **(Goyens et al., 2005)**. Alpha Linolenic Acid (ALA) is the principal n-3 fatty acid, which a healthy human will convert into eicosapentanoic acid (EPA), and later into docosahexaenoic acid (DHA) **(Charles et al., 2006 and Julius, 2006)**.

2. 2. Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA).

Polyunsaturated fatty acids (PUFA), including DHA and also DPA and eicosapentaenoic acid (EPA) (20:5) are natural constituents of the human diet. The main dietary source of these PUFA are fish, particularly fatty fish such as haddock, tuna, salmon, and mackerel, in which concentrations of total omega-3 fatty acids range from 0.1 to 5.3 g/100 g **(Sanders, 1989)**. EPA and DHA are formed in animal (including fish and shellfish) tissues, but not plant tissues which are usual sources of α-linolenic acid. DHA is a component of membrane structural lipids that are enriched in certain phospholipids components of the retina and nonmyelin membranes of the nervous system. EPA is a precursor of the omega-3 eicosanoids **(Kinsella et al., 1990**). EPA is found in cholesterol esters, triglycerides and phospholipids. DHA is found mostly in phospholipids and is one of the most abundant components of the brain's structural lipids **(Teitelbaum and Walker, 2001)**. Fish consumption is largely recognized as beneficial for brain development and protective against cardiovascular diseases, mental disorders and various inflammatory conditions such as bowel diseases, asthma, and arthritis. Long-chain omega-3 polyunsaturated fatty acids (n-3 PUFA), more specifically eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are believed to be responsible for these beneficial effects **(Uauy et al., 2001)**. The fatty fish are high in two kinds of omega-3 polyunsaturated fatty acids (PUFA): eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). It has been estimated that consumption of one fatty fish meal per day could result in an omega-3 fatty acid intake (i.e., EPA and DHA) of approximately 900 mg/day **(Kris-Etherton et al., 2002)**. The conversion of ALA to eicosapentaenoic acid (20:5 n3, EPA) and docosahexaenoic acid (22:6 n3, DHA) is inefficient in marine fish, which have high concentrations of LC-PUFA in their natural diet. Conversion is greater in freshwater fish, which have high concentrations of LA and ALA and limited DHA in their natural diet **(Sargent et al., 2002)**. The fatty acids of fish lipids are rich in n-3 long chain, highly unsaturated fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) that have particularly important roles in animal nutrition, including fish and human nutrition, reflecting their roles in critical physiological processes **Tocher, (2003)**. Salmon is one of the fatty fish included in the list of species high in two kinds of omega-3 fatty acids, eicosapentaenoic acid (EPA) and docosohexaenoic acid (DHA) **(Gagnon et al., 2004**). Long-chain omega-3 polyunsaturated fatty acids (n-3 PUFA), more specifically eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are believed to be responsible for these beneficial effects **(Ruxton et al., 2004)**. Foods enriched with EPA and DHA or fish oil supplements are a suitable alternate to achieve recommended intakes and may be necessary to achieve intakes of 1 g/d **(Gebauer et al., 2006)**. EPA and the GLA synthesized from linoleic (n-6) acid are later converted into hormone-like compounds known as eicosanoids, which aid in many bodily functions including vital organ function and intracellular activity **Julius, (2006)**.

3. Role of omega 3 fatty acids family in human health.

3.1. Bad effect of high fat diet on human health.

The composition of plasma and tissue lipids in man and animals is a reflection of the type and amount of dietary lipids consumed **(Loo et al., 1991)**. Diets high in fat content induce rapid weight gain, obesity, and insulin resistance in rats, mice, and humans **(Thomas et al., 1992 and Guo and Jen, 1995)**. Saturated fatty acids could be increasing the synthesis of LDL and /or decreasing the LDL fractional catabolic rate **(Barr et al., (1992) and Oberman et al., (1993).** The dietary fats producing elevation in saturated fatty acids have been shown to be composed principally of coconut oil or animal fat such as butter, beef tallow, and lard. These fats are relatively saturated their hypercholesterolemic effect is complicated by the presence of variable amounts of cholesterol or saturated fatty acids of short and intermediate chain length **(Nicolosi, 1997).** High-fat-diets induce several obesity related metabolic deteriorations, including liver lipid infiltration, which is now recognized as an integral feature of the metabolic syndrome **Satia-Abouta et al., (2002)**. Hyperlipidemia (mainly increased level of cholesterol or low density lipoprotein (LDL)-cholesterol) is an important risk factor in the initiation and progression of atherosclerotic lesions **(Harrison et al., 2003, Taha et al., 2004 and Ramadan et al., 2011)**. Fat-enriched diets have been used for decades to model obesity, and insulin intolerance in rodents. It has been observed that the disorders achieved by high-fat feeding resemble the human metabolic syndrome closely, and this also may extend to the cardiovascular complications **(Woods et al., 2003)**. The high-fat intake itself can contribute to the development of obesity and hyperlipidemia in human and rodents by altering cholesterol and triglyceride levels in plasma and tissues **(Srinivasan et al., (2004), Rajlakshmi and Sharma, 2004 and Lee et al., 2006)**.

3.2. Role of omega 3 fatty acids family on different diseases.

Omega-3 fatty acids are an important component of cell membranes and their phospholipids. Every cell membrane consists of two layers of phospholipids (Omega-3s and other lipids) and cholesterol. Between these two layers are proteins acting as receptors, transporters, and enzymes. The phospholipid composition determines the physical and functional properties of cell membranes and has critical implications for cell integrity, growth, immunity, and anti-inflammatory properties **(Artemis et al., 1986)**. The clinical conditions such as cardiovascular disease, blood pressure, cancer, skin diseases and immune disorders such as renal failure, rheumatoid arthritis and multiple sclerosis may be prevented by ALA in flaxseed oil **(Kelley et al., 1991**). The results from various animal and human epidemiologic studies have led to the hypothesis that fish oil rich in n-3 PUFA prevents atherosclerosis **(Kim et al., 1991)**. Omega-3 fatty acids are essential for normal growth and development and may play an important role in the prevention and treatment of coronary artery disease, hypertension, diabetes, arthritis, other inflammatory and autoimmune disorders, and cancer **(Simopoulos, 1991)**. The omega-3 fatty acids play an important role in modulation and prevention of human disease, particularly ischemic heart disease. Consumption of dietary omega-3 fatty acids has been found to reduce the risk after myocardial infarction and to prevent sudden death and cardiac arrest in prospective epidemiological studies **(Kromhout et al., 1995**). In humans, that an increase in the ingestion of long-chain polyunsaturated fatty acids (LC-PUFA), especially EPA and DHA, in diet reduces the risk of heart disease and rheumatoid arthritis **(Steffens, 1997)**. The clinical studies indicate that LC omega-3 PUFA supplementation showed cardioprotective effects in people with type 2 diabetes without any side effects on glucose control and insulin activity **(Sirtori et al., 1998)**. The eicosanoids derived from omega-3 are predominantly anti inflammatory and inhibit platelet aggregation **(Simopoulos, 1999)**. The consumption of LC-PUFA and fish oils is asserted to reduce the biochemical factors associated with cancer **(Kimura, 2001**). Omega-3 polyunsaturated fatty acid (PUFA) deficiency, induced by feeding a diet enriched in omega 6 PUFA and low in omega 3 PUFA, in the perinatal period was associated with increased blood pressure later in life. The experiment showed that Sprague-Dawley rat pups raised up to the age of 9 weeks on an omega-3 PUFA deficient diet and then fed a control diet containing alpha-linolenic acid (ALA) for the next 24 weeks had higher blood pressure than rats provided with dietary ALA for their entire lives **Armitage et al., (2003)**. The metabolism of fatty acids of the n-3 family is of particular interest because of the biological actions of their metabolites (eicosanoids) in vivo. For example eicosanoids derived from n-3 PUFA tend to inhibit platelet aggregation and be anti-inflammatory **(Lee and Lip, 2003)**. The epidemiological studies as well as dietary trials including moderate amounts of ALA in the experimental diet suggest that this essential fatty acid, despite its low concentrations in blood and tissues, may be important in relation with the pathogenesis (and prevention) of CHD **(De Lorgeril, and Salen, 2004)**. It is still not known whether ALA is cardioprotective by itself only or also through its conversion in long-chain (n-3) PUFA and then in the corresponding eicosanoids and prostaglandins. The notion that omega-3 fatty acids may be effective dietary supplements in the management of various diseases in which oxidant/antioxidant defense mechanisms are decelerated **(Erdogan et al., 2004)**. The preliminary animal study provides strong support for a therapeutic effect of n-3 EFA in some neuropsychiatric disorders in which reactive oxygen species (ROS) are recently accused to be an important physiopathogenetic factor **(Songur et al., 2004)**. The omega 6–3 PUFA imbalance early in life leads to irreversible changes in hypothalamic composition. The increased ALA and reduced DHA proportions in the animals re-fed ALA in later life are consistent with a dysfunction or down-regulation of the conversion of ALA to 18:4n-3 by the delta-6 desaturase **(Li et al., 2006)**. Polyunsaturated fatty acids (PUFA) especially omega 3 fatty acids can reduce blood LDL cholesterol and have antithrombotic, antiinflammatory, antiarrhythmic and vasodilatory properties. Hence, PUFA may help to prevent coronary heart disease, hypertension, type 2 diabetes and insulin resistance **Lombardo and Chicco, (2006)**.

3.3. Role of omega 3 fatty acids family as hypolipidemic agent on coronary heart diseases.

The relationship between dietary omega-3 fatty acids and risk of developing cardiovascular disease (CVD) began to emerge in the late 1970s **(Bang et al., 1980)**. The mechanism that explains the hypotriglyceridemic effect of fish oil is related mainly to the reduction of hepatic very low-density lipoprotein (VLDL) synthesis and secretion **(Harris et al., 1990)**. The fish oils are relatively rich in n-3 fatty acids. The two most common, eicosapentaenoic acid (20:5n3) and docosahexaenoic acid (22:6n3), are involved in many biological processes. Fish oil supplementation has been shown to have a protective effect against atherosclerotic changes by lowering plasma triacylglycerols and lipoprotein (especially very-low-density lipoprotein) concentration in normal as well as in hypertriglyceridemic men **(Kinsella et al., 1990**). The beneficial effects of ALA on plasma lipid and lipoproteins are more controversial; it has been reported to decrease in total cholesterol (TC), LDL-cholesterol (LDL-C), LDL-C/HDL-C **(Cunnane et al., 1993)**. The fish consumption or dietary intakes of fish oil reduce the risk of death, especially caused by coronary heart disease **(Daviglus et al., 1997)**. Omega 3 fatty acids, including ALA, are reported to lower serum cholesterol and triglyceride levels **(Craig, 1999)**. Supplementing food with (n-3) fatty acids in the normal diet has been proved beneficial in reduction of cardiovascular disease in those who consume diet containing deep-water fish and fish oil

Siscovick et al., (2000). Omega 3 fatty acids have important role in the modulation and prevention of human diseases, particularly coronary heart disease **(William, 2000)**. In subjects with hyperlipidemia intake of bread containing a small amount of fish oil results in a significant increase in omega-3 fatty acids, an increase in HDL-cholesterol, and a decrease in triglycerides, which may reduce the risk of ischemic heart disease **Liu et al., (2001**). The high combined dietary intake of EPA and DHA and possibly ALA, may lower the risk of coronary patients to get fatal event **(Lemaitre et al., 2003)**. Omega-3 PUFA can reduce the progression of atherosclerosis because of their anti-inflammatory properties and effects on atherogenesis in the arterial wall **(Yaqoob, and Calder, 2003)**. The high content of the polyunsaturated fatty acids (PUFA) such as EPA and DHA in marine lipids is thought to play a positive role in reducing the risk of cardiovascular diseases **(Harris and Schacky, 2004 and Jehangir et al., 2004**). The chia diets dramatically decreased triacylglycerol levels and increased HDL cholesterol and n-3 fatty acid contents in rat serum. These findings suggest that a-linolenic–rich chia oil may be an alternative to n-3 sources for vegetarians and people allergic to fish and fish products **Ayerza and Coates, (2005**). The n-3 fatty acids are used in the formation of cell walls, making them supple and flexible, and improving circulation and oxygen uptake with proper red blood cell flexibility and function. n-3 fatty acids deficiencies are linked to decreased memory and mental abilities, tingling sensation of the nerves, poor vision, increased tendency to form blood clots, diminished immune function, increased triglycerides and "bad" cholesterol (LDL) levels, impaired membrane function, hypertension, irregular heart beat, learning disorders, menopausal discomfort, itchiness on the front of the lower leg(s), and growth retardation in infants, children, and pregnant women **(Julius, 2006)**. The dietary recommendations have been made for n-3 fatty acids, including alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) to achieve nutrient adequacy and to prevent and treat cardiovascular disease. These recommendations are based on a large body of evidence from epidemiologic and controlled clinical studies. The n-3 fatty acid recommendation to achieve nutritional adequacy, defined as the amount necessary to prevent deficiency symptoms, is 0.6–1.2% of energy for ALA; up to 10% of this can be provided by EPA or DHA. To achieve recommended ALA intakes, food sources including flaxseed and flaxseed oil, walnuts and walnut oil, and canola oil are recommended. The evidence base supports a dietary recommendation of approximately 500 mg/d of EPA and DHA for cardiovascular disease risk reduction **(Levenson and Axelrad, 2006)**. The n-3 PUFA in the form of fish oil or capsules containing the purified n−3 PUFA can have a place in the newest guidelines of AHA (American Heart Association) for ischemic coronary heart disease. The use of one gram of EPA+DHA a day (2–4 g in patients with hypertriglyceridemia) as a cardiovascular preventive dose seems reasonable **(Lichtenstein et al., 2006)**. Influence of n−3 PUFAs on serum lipid levels, mainly their effect on triglycerides is mostly linked with elevation of HDL-cholesterol **Fedacko et al., (2007**). Both purslane seed and flaxseed oils reduced total cholesterol and LDL-cholesterol in rats feed on high fat diets (**Ashoush et al., 2009).**

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