Review article

n-3 Omega fatty acids: a review of current knowledge

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Summary The very long chain polyunsaturated fatty acids (PUFAs) (C18–C22) and n-3 Omega PUFAs are apparently widely accepted as a part of modern nutrition because of their beneficial effects on metabolism. Most significantly, the reported protective effect of the n-3 omega fatty acids in relation to cardiovascular inflammatory diseases and cancer has led people to consider these fatty acids more beneficial than other dietary supplements. Unfortunately, there is a lack of studies relating to the physical performance increasing effect in sports diets, cholesterol-reducing effect in meat technology, effects on human serum profile, the application dose and the side effects with/without omega-6 PUFAs, which has left us with several crucial unanswered questions. We still do not know the correct dose of n-3 omega and the correct ratio of n-3 omega to n-6 omega or their possible contraindications when combined with drugs, other foods and herbal supplements. Another reported aspect of n-3 omega PUFAs is that they protect and even enhance the effect in medical treatment of important diseases such as Alzheimer’s, multiple sclerosis and cancer. These reports led to PUFAs becoming one of the most accepted and consumed food supplements. Despite this weight of evidence and the considerable current use, there is still a need for studies, which will determine whether the n-3 omega fatty acids are in fact important functional supplements with no adverse effects. This review will attempt to outline the current position of n-3 omega fatty acids in the field of clinical nutrition and healthcare and outline the studies needed to determine whether there are significant advantages in taking them as food supplement without any adverse effects.

Keywords Food, n-3 omega fatty acids, nutrition, public health and disease, polyunsaturated fatty acid.

Introduction

n-3 Omega polyunsaturated fatty acids (PUFAs) are long chain PUFAs found in plants and marine sources such as fish, mussel, oyster, shrimp but primarily cold water fish (Friedman & Moe, 2006) but also exist in a wide range of plant products such as nuts, especially English walnuts, seeds, namely sesame (Namiki, 2007), flax seed and vegetable oils such as soybean and canola besides olive (Whelan & Rust, 2006). n-3 Omega fatty acids, unlike saturated fatty acids, have been associated with various health benefits relating to treatment of rheumatoid arthritis (Rennie et al., 2003) and coronary artery disease (Freeman, 2000) whilst improving blood pressure control and preserve renal function even in hypertensive heart transplant recipients (Holm et al., 2001). The effects of n-3 omega PUFAs on various cancers and also on other clinical disorders including oedema, rheumatoid arthritis, cardiovascular disease and others, is closely related to their metabolism.

Hence replacement of saturated fat with unsaturated fatty acids for the protection against metabolic diseases and disorders, n-3 omega PUFAs have been widely accepted as one of the cornerstones of healthy lifestyle and nutrition.

This review attempts to bring together current information in respect of the biochemistry, clinical effects and nutritional advantages of n-3 omega PUFA. The material is divided into three sections dealing with:

1. The identification of long chain polyunsaturated fatty acids, n-3 omega PUFAs and n-6 omega PUFAs. In its first part, entitled ‘Metabolic pathways of omega PUFAs’, the relationship between the consumption of n-3 and n-6 omega PUFAs and production of inflammatory cytokines, namely thromboxane and leukotriene by Prostaglandin hormones are discussed;

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2. The evidence and scientific data as related to the association of n-3 omega PUFAs with various important metabolic diseases, relation between the consumption of n-3 and n-6 omega PUFAs and production of inflammatory cytokines namely thromboxane and leukotriene by Prostaglandin hormones. In this part, the evidence and scientific data as related to the association of n-3 omega PUFAs with various important metabolic diseases was given and evaluated. Relationships between n-3 omega PUFAs and diseases, the effects of n-3 omega PUFAs on diseases in saturated fat and cholesterol origin, cancer, neurologic diseases and disorders such as schizophrenia, depression, anxiety, postpartum depression and Alzheimer’s Disease (AD) and visual disorders, were evaluated under the available highlight of related scientific evidence; and

3. Some outstanding questions as related to the necessity of combined use of n-3 Omega PUFAs and a fat soluble vitamin, the minimum effective dose, recommended daily intake, energy increasing potential in sports and postoperative periods, their oxidation potential in spite of claims which indicate to their antioxidant effect, their effect on low density lipoprotein (LDL, bad cholesterol) oxidation, their increasing effect on meat oxidation, their form in stronger effect and their effect on bone and skeletal health and nerve health, their adverse effect in patients with heart disease, and side effects of their mega doses – all these questions were discussed in this part, followed by the studies which should be performed to highlight the questions about n-3 omega PUFAs were addressed.

Identification of PUFAs

The very long chain PUFAs (C18, C20 and C22) include the two essential fatty acids; linoleic acid (LA) [18:2 (n-6 omega)] and α-linolenic acid (α-LN) [18:3 (n-3 omega)] and are most commonly found in large amounts in some certain fish species (Poisson, 1990). These two essential fatty acids (EFAs) are the only sources for the production of important longer chain PUFAs such as prostaglandins; dynamic but short lived compounds that control blood vessels and other body functions. Arachidonic acid (AA) (20:4 n-6) (Pereira et al., 2004), a member of the n-6 PUFA, is another source of prostaglandins (PG). Eicosapentaenoic acid (EPA) (20:5 n-3), LN and docosahexaenoic acid (DHA) (C22) EFAs are called three PUFAs or n-3 omega PUFAs (n-3 series) (Pereira et al., 2004). In addition, dietary LN can be converted to the EPA and DHA. AA, LN and LA, long chain and highly unsaturated fatty acids are truly essential, while C18 compounds, stearic and palmitic acids, abundant in animal fat, should be considered as conditionally essential (Trautwein, 2001).

Metabolic pathways of n-3 omega PUFAs

Consumption of lipid emulsions rich in omega 6 PUFAs (LA and AA) leads to an increased amount of dienoic prostaglandin E2 (PGE2) (a group of hormone -like substances that participate in a wide range of bodily functions such as contraction and relaxation of smooth muscles, dilation and constriction of blood vessels, control of blood pressure and modulation of inflammation), thromboxane (a lipid which constricts blood vessels and is produced in platelets) and leukotriene (a lipid responsible for the effects of inflammatory response by the production of histamine) production as a result of the metabolic breakdown of AA. PGE2 production from AA is catalysed by a key membrane-bound enzyme, Prostaglandin endoperoxidase synthase (PGhs). Thromboxane A2, which is produced by Pghs2, is responsible for vascular permeability, platelet aggregation and oedema (Kramer et al., 1996; Tapiero et al., 2002). PGE2, thromboxanes (especially thromboxane A2) and leukotrienes are responsible for their immunosuppressive properties and for the generation of free oxygen radicals. Briefly, inflammation and thrombogenesis rates are mainly controlled by n-6 PUFAs (LA and AA). In contrast, emulsions rich in EPA, LN and DHA (n-3 omega PUFAs) inhibit the breakdown of AA, which is produced by the synthesis of PGE2 (Fig. 1). This group (LN and dihomo ω-LN) produces PGE1, a hormone in lipid origin which has got beneficial effects on the body, opposite to those of PGE2, such as regulation of calcium movement, controlling hormone regulation and cell growth, PGE3 and PG13, PGE3 and PG13 have got beneficial effects similar to those of PGE1, such as inhibiting inflammation and increasing trienoic PGs, thromboxane A3 and pentaenoic leukotrienes (e.g. LTB5) (Trautwein, 2001). PGD2, a prostaglandin which is only found in the brain and mast cells, is critical to the development of allergic diseases and is involved in the regulation of reducing body temperature, in sleep, acts as an opposite to PGE2. But, PGE2, produced by n-6 omega PUFAs, has an awakening effect (Yehuda et al., 1999). PGE1, E3 and I3 inhibit the inflammatory reactions, as opposed to PGE2, while thromboxane A3 decreases platelet activation and thrombogenesis rate as opposed to thromboxane A2 which is produced by n-6 omega PUFAs (Fig. 1).

Simply stated, n-3 omega PUFAs lower the risk of inflammation and thrombogenesis caused by n-6 omega PUFAs (Nitenberg & Raynard, 2000). Dietary LN is rapidly converted to another n-3 omega (dihomo ω-LN), which can then be converted to n-6 AA.

Since AA is the precursor of the inflammatory agents such as PGE2, cytokines, interleukin-1 (IL-1), interleukin-2 (IL-2), interleukin-6 (IL-6) and dihomo ω-LN is the precursor of the anti-inflammatory 1-series eicosanoids (Fig. 1) such as PGE1 (Endres et al., 1989;
Yehuda et al., 1999), it is not only the ratio of AA to dihomo α-LN or LN, but also the conversion rate of these fatty acids to each other, which is the significant factor in predicting whether there will be inflammation in the future (Belluzzi, 2001). Dihomo α-LN and LN (as n-3 omega PUFA) also inhibit inflammation by reducing the production of inflammatory PGE2, leukotriene B4 (LTB4), IL-1, IL-2 and IL-6 (Santoli et al., 1990; Baker et al., 2005).

**The association of n-3 omega PUFAs with diseases**

n-3 Omega PUFAs, inflammatory diseases, diseases in cholesterol, saturated fat and sugar origin (Fig. 2, Fig. 3)

The anti-inflammatory properties of n-3 omega PUFAs are used in the treatment of inflammatory diseases such as inflammatory bowel disease (IBD), eczema, psoriasis and rheumatoid arthritis (Cleland et al., 2003). Similarly,
an increase in n-6 omega PUFAs and a decrease in n-3 omega PUFAs raises the rate of occurrence of Crohn’s disease (inflammation of colon). Inhibition of the proinflammatory cytokine (proteins, peptides or glyco-proteins that are produced widely by cells throughout the body cells which are critical to the development and functioning of the immune response by activating immune cells to increase the systems response to the pathogen) synthesis by n-3 omega PUFAs can therefore be beneficially used in the treatment of Crohn’s disease (Griffiths, 1998). Treatment of such diseases with n-3 omega PUFAs also reduces mucosal damage caused by inflammation or by Crohn’s disease. Stenson et al. (1992) and Hawthorne et al. (1992) have treated ulcerative colitis with first 5.4 g and then 4.5 g of n-3 omega PUFAs (fish oil) and observed significant healing of the colon mucosa. The effects of leukotrienes which are proinflammatory mediators which can lead to post-traumatic immune dysregulation, can also be mediated by n-3 omega PUFA supplementation in the postoperative period. Thus, n-3 omega PUFAs are important anti-inflammatory agents in the postoperative periods (Köller et al., 2003). Additionally, n-3 omega PUFAs, DHA and EPA, were found as to have different in the effects on leucocyte functions such as phagocytosis, chemotactic response and cytokine production. For example, DHA has got an increasing effect in neutrophil proliferation and monocyte phagocytosis while EPA does not have got the same effect (Gorjao et al., 2009).

The supplementation of the standard diet with key nutrients which have immunomodulatory properties such as arginine, omega 3 fatty acids and glutamine (the most abundant non-essential amino acid in body) control the surgery-induced immunosuppression and hyperinflammation effectively (Gianotti et al., 2003). The administration of n-3 omega PUFAs ameliorates the host defence mechanisms, controlling the inflammatory response, not only in postoperative but also in the preoperative periods (Braga et al., 1998). Chen & Yeh (2003) reviewed the beneficial effects of administering by injection of omega 3, in the form of fish oil and indicated the importance of these effects. They showed that incorporation of the omega 3 into the cellular membranes of many cell populations can consequently influence the disease process, lead to a decrease in platelet aggregation and thrombosis or ameliorate the

### Table 1 The list of PUFAs

<table>
<thead>
<tr>
<th>Name</th>
<th>Lipid name</th>
<th>Chemical name</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\alpha)-Linolenic acid ((\alpha)-LN)</td>
<td>18:3 (n-3)</td>
<td>all-cis-9,12,15-ortadacatrienoic acid</td>
</tr>
<tr>
<td>Stearidonic acid (STD)</td>
<td>18:4 (n-3)</td>
<td>all-cis-6,9,12,15-octadecatetraenoic acid</td>
</tr>
<tr>
<td>Eicosatrienoic acid (ETE)</td>
<td>20:3 (n-3)</td>
<td>all-cis-11,14,17-eicosatrienoic acid</td>
</tr>
<tr>
<td>Eicosatetraenoic acid (ETA)</td>
<td>20:4 (n-3)</td>
<td>all-cis-8,11,14,17-eicosatetraenoic acid</td>
</tr>
<tr>
<td>Eicosapentaenoic acid (EPA)</td>
<td>20:5 (n-3)</td>
<td>all-cis-5,8,11,14,17-eicosapentaenoic acid</td>
</tr>
<tr>
<td>Docosapentaenoic acid (DPA)</td>
<td>22:5 (n-3)</td>
<td>all-cis-7,10,13,16,19-docosapentaenoic acid</td>
</tr>
<tr>
<td>Docosahexaenoic acid (DHA)</td>
<td>22:6 (n-3)</td>
<td>all-cis-4,7,10,13,16,19-docosahexaenoic acid</td>
</tr>
<tr>
<td>Tetracosapentaenoic acid</td>
<td>24:5 (n-3)</td>
<td>all-cis-9,12,15,18,21-tetracosapentaenoic acid</td>
</tr>
<tr>
<td>Tetracosahexaenoic acid</td>
<td>24:6 (n-3)</td>
<td>all-cis-6,9,12,15,18,21-tetracosahexaenoic acid</td>
</tr>
</tbody>
</table>


![Figure 3 Linolenic (LN) and palmitic acid contents (g 100 g\(^{-1}\)) of some foods.](image)
disease process in certain conditions and reduce accumulation of lipid peroxidation products in liver. Confirming these findings, DHA and EPA were found to serve as substrate for the production of the anti-inflammatory compounds such as resolvins and protectins while inhibiting the activation of nuclear factors that induce inflammation (nuclear factor kappa B and interleukins) (Goldberg & Katz, 2007). The meta-analysis made by them to examine the pain relieving effects of EPA and DHA in patients with rheumatoid arthritis or joint pain secondary to inflammatory bowel disease or dysmenorrhoea (severe uterine pain during menstruation) supports the premise that n-3 omega PUFAs (EPA and DHA) may decrease the pain experience in the patients.

Cardiovascular disease and n-3 omega PUFAs

Besides the anti-inflammatory effect of n-3 omega PUFAs, the other beneficial and protective effect of these fatty acids is on the cardiovascular system. Trans fatty acids, cholesterol and saturated fats are mainly responsible for atherosclerosis. On the contrary, n-3 omega PUFAs are beneficial in reducing cholesterol and thus the risk of myocardial infarction (Zyriax & Windler, 2000). Another cause of cardiovascular disease formation is the hypertriglyceridaemia, an increase in the serum triglyceride in blood serum level, can also be reduced by the addition of n-3 omega (fish oil) to the diet (Hau et al., 1996). The modern sciences of dietetics and nutrition studies the relationship between nutrition and health so that people can protect themselves from diseases or ameliorate the adverse effects of these diseases by means of appropriate diets (Table 1). The many close relationships between ‘a high selenium intake and a lower incidence rate of cancer’ (Borek, 2004; Diwadkar-Navsariwaka & Diamond, 2004; Jacobs et al., 2004; Charalabopoulos et al., 2006) despite conflicting evidence of no effect (Clark et al., 1996),

Table 2 Amounts (g) of some foods which should be consumed to provide 1 g EPA and DHA

<table>
<thead>
<tr>
<th>Fish/sea food</th>
<th>Gram day⁻¹ to provide 1 g EPA and DHA per day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fresh tuna</td>
<td>70-360</td>
</tr>
<tr>
<td>Sardines</td>
<td>60-90</td>
</tr>
<tr>
<td>Salmon</td>
<td>60-135</td>
</tr>
<tr>
<td>Mackerel</td>
<td>60-250</td>
</tr>
<tr>
<td>Herring</td>
<td>45-60</td>
</tr>
<tr>
<td>Rainbow trout</td>
<td>90-105</td>
</tr>
<tr>
<td>Halibut</td>
<td>90-225</td>
</tr>
<tr>
<td>Cod</td>
<td>375-750</td>
</tr>
<tr>
<td>Haddock</td>
<td>450</td>
</tr>
<tr>
<td>Catfish</td>
<td>450-600</td>
</tr>
<tr>
<td>Flounder</td>
<td>210</td>
</tr>
<tr>
<td>Oyster (Pacific/eastern/farmed)</td>
<td>75/195/240</td>
</tr>
<tr>
<td>Lobster</td>
<td>225</td>
</tr>
<tr>
<td>Crab, Alaska King</td>
<td>255</td>
</tr>
<tr>
<td>Shrimp</td>
<td>330</td>
</tr>
<tr>
<td>Clam</td>
<td>375</td>
</tr>
<tr>
<td>Scallop</td>
<td>525</td>
</tr>
</tbody>
</table>


Table 3 Fat content/EPA + DHA (g 100 g⁻¹) and fat content/α-linolenic acid (g 100 g⁻¹) ratio of some various fish, marine products, vegetables and oils

<table>
<thead>
<tr>
<th>Fish/sea food</th>
<th>Fat content (g 100 g⁻¹)</th>
<th>EPA + DHA (g 100 g⁻¹)</th>
<th>Fat content (EPA + DHA) (g 100 g⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eel</td>
<td>24.5</td>
<td>0.83</td>
<td>29.51</td>
</tr>
<tr>
<td>Herring</td>
<td>17.8</td>
<td>2.72</td>
<td>6.54</td>
</tr>
<tr>
<td>Sprat</td>
<td>16.6</td>
<td>3.23</td>
<td>5.14</td>
</tr>
<tr>
<td>Tuna</td>
<td>15.5</td>
<td>3.37</td>
<td>4.60</td>
</tr>
<tr>
<td>Salmon</td>
<td>13.6</td>
<td>2.86</td>
<td>4.76</td>
</tr>
<tr>
<td>Mackerel</td>
<td>11.9</td>
<td>1.75</td>
<td>6.8</td>
</tr>
<tr>
<td>Carp</td>
<td>4.8</td>
<td>0.30</td>
<td>16</td>
</tr>
<tr>
<td>Sardine</td>
<td>4.5</td>
<td>1.39</td>
<td>3.24*</td>
</tr>
<tr>
<td>Swordfish</td>
<td>4.4</td>
<td>1.79</td>
<td>2.45*</td>
</tr>
<tr>
<td>Trout</td>
<td>2.7</td>
<td>0.59</td>
<td>4.58</td>
</tr>
<tr>
<td>Halibut</td>
<td>1.7</td>
<td>0.51</td>
<td>3.33*</td>
</tr>
<tr>
<td>Cod</td>
<td>0.6</td>
<td>0.18</td>
<td>3.33*</td>
</tr>
<tr>
<td>Haddock</td>
<td>0.6</td>
<td>0.16</td>
<td>3.75*</td>
</tr>
<tr>
<td>Lobster</td>
<td>1.9</td>
<td>0.20</td>
<td>9.5</td>
</tr>
<tr>
<td>Shrimp</td>
<td>1.4</td>
<td>0.30</td>
<td>4.66</td>
</tr>
<tr>
<td>Muscles</td>
<td>1.4</td>
<td>0.15</td>
<td>9.33</td>
</tr>
<tr>
<td>Anchovy</td>
<td>2.3</td>
<td>0.50</td>
<td>4.60</td>
</tr>
<tr>
<td>Sardine</td>
<td>13.9</td>
<td>2.44</td>
<td>5.70</td>
</tr>
</tbody>
</table>

Source: Sauci et al. (1994).

*Food which appears as perfect from the point of omega 3 content.
'high carotenoid intakes and lower risk of cancer' (Mannisto et al., 2004), 'dietary fat, high amounts of animal, saturated and trans fat intakes and obesity' (Bray & Popkin, 1998; Field et al., 2007), 'high dietary sodium intake and increase in the risk of hypertension' (de Wardener et al., 2004; Adroge & Madrias, 2007), 'high alcohol intake and stroke risk' (Reynolds, 2003) have been proven and similarly the close link between omega 3 PUFAs and cardiovascular disease is now widely accepted (Temple, 2002). According to Harris et al. (2003), of all known dietary factors, long-chain omega 3 fatty acids may be the most protective against death from coronary heart disease (CHD), by increasing the n-3 omega intake of an individual with coronary artery disease by approximately 1 g day\textsuperscript{-1} (Tables 2 and 3). The best prevention of cardiovascular diseases appears to be achieved by replacing saturated fats with n-3 omega PUFAs (Temple, 1996). Such replacement appears to have a direct effect on the intrinsic ability of a cardiac muscle fibre to contract at a given fibre length. These effects indicate to the beneficial and protective effects of omega 3 fatty acids in preventing sudden death following myocardial infarction (Bhatnagar & Durrington, 2003). Eicosanoid synthesis from n-3 omega PUFAs minimises the production of PGE2 and thromboxane A2, IL-1, IL-2 and IL-6 (Fig. 1). Specifically, minimising the production of thromboxane A2 and IL-1, IL-2 and IL-6 by n-3 omega PUFAs protects the individual’s health by protecting cardiac tissue from clot formation, platelet aggregation and thrombosis risk (Arkhipenko & Sazantova, Arkhipenko & Sazontova, 1995; Wahlqvist, 1998). A further benefit for the cardiovascular system is the lowering of total cholesterol by n-3 omega PUFAs (Kusunoki et al., 2003). Indeed, daily supplementations of 3 g in men and EPA containing soy phospholipid at 10% level in rat can decrease total serum cholesterol and LDL (bad cholesterol, which sticks free cholesterol in blood onto the walls of blood vessels) whilst slightly increasing high density lipoprotein (HDL: good cholesterol, which is claimed as protective against hypertension and calcification) (Lox, 1990) (HDL: good cholesterol, which is claimed as protective against hypertension and calcification since it can take bound cholesterol from the walls of vessels and return it to blood stream). Supportive data is found in a study in rats in which a soybean oil containing 5% EPA showed a significant decrease in serum triglyceride (TG) levels (Dasgupta & Bhattacharyya, 2007).

Although most studies define n-3 omega PUFAs as lowering cholesterol and LDL as reducers, a few studies suggest that long term use of n-3 omega PUFAs results in increase in LDL. Schacky et al. (1999) found a 7% increase in LDL, following a period of 2 years during which subjects consumed 3 g of EPA and DHA daily. Similarly, 3 g 7 kg\textsuperscript{-1} 7 day\textsuperscript{-1} use of EPA and DHA, was shown to lower the amount of VLDL (Very Low Density Lipoprotein, which is claimed as more harmful than LDL because of its greater ability to bind free cholesterol on to the walls of blood vessels), while enhancing the production rate of LDL. The decrease in VLDL and increase in LDL seem to be due to the conversion of VLDL to LDL by postheparin lipase, an enzyme of the hydrolase class which shows its activity in the endothelial surface in mammary, muscle and adipose tissues and is activated by n-3 omega PUFAs (Lu et al., 1999). However, despite this increase of LDL, Schacky et al. (1999) found a slight mitigation of the progress of atherosclerosis. The cholesterol reducing and HDL increasing effect of n-3 omega PUFAs makes them one of the most effective substances in the prevention of atherosclerosis, comparable to niacin, statins, and fibres (Barbeau et al., 1997; Rader, 2003). n-3 Omega PUFA supplementation of the diet has also been seen to lower the blood pressure in rats (Yahia et al., 2003). Similarly, n-3 omega rich rapeseed oil supplementation also has a reducing effect on cholesterol and the ratio of LDL to HDL (Eder & Brandsch, 2002). Li (2003) has supported these findings by confirming the beneficial effects of these fatty acids on systolic and diastolic blood pressure and stroke. This beneficial effect of n-3 omega PUFAs has attracted the attention of humanity in this new millennium and appropriately, the aeronautical industry is employing PUFAs to protect the cardiovascular systems of astronauts against the abnormal and extraordinary oxidative stress of space (Turner et al., 2002).

The protective effect of n-3 omega PUFAs on the cardiovascular system, can easily be increased by niacin, bile acid, resins, sport and exercise, which highlights the importance of lifestyle and nutrition on health. Similarly, increased intakes of marine n-3 omega PUFAs can result in decreased triglycerides, fibrinogen and platelet aggregation, which are considered to be beneficial for cardiovascular diseases (Wijendran & Hayes, 2004). It was found in a study by Sweeney et al. (1999) that Japanese students who had relocated to USA showed higher serum triglyceride, cholesterol levels and a high risk of cardiovascular diseases when compared with the general population of Japan. The apparent explanation of this difference is that the native Japanese diet is high in n 3-omega PUFAs whilst the American diet is not. The fact that higher serum triglyceride, cholesterol levels and high risk of cardiovascular diseases found in Japanese students, following their moving to the USA, can be compared with the lower triglyceride and cholesterol levels of the general population of Japan, is a clear example, showing the significance of n-3 omega fatty acids as cardio protectors (Sweeney et al., 1999). Liu et al. (2001) added n-3 omega PUFAs to bread, as one of the most commonly consumed food products and this enrichment lowered serum triglyceride level and also total serum cholesterol by increasing HDL. Russo (2009) recommends the intake of 1 g day\textsuperscript{-1} of EPA and DHA for treatment of post Myocardial Infarction.
(MI) and prevention of sudden cardiac death and other cardiovascular dysfunctions. n-3 Omega PUFAs also inhibit protein kinase C and increase in nitrous oxide (NO) release, which inhibits platelet adherence to the collagen and thus eases blood circulation (Schoene, 2001; El-seweidy et al., 2002). Thus, supplementation of the diet with n-3 omega PUFAs is very effective and protective against cardiovascular diseases, such as hypertension and atherosclerosis (Shoda et al., 1996; Temple, 2002) and even in the reduction of the incidence of sudden cardiac death (Villa et al., 2002). n-3 Omega supplementation of the diet of rats, decreased the mortality rate, caused by myocardial infarction (MI) while decreasing creatine phosphokinase as the indicator for MI. In contrast, an increased mortality rate was observed when the rat diets were supplemented by saturated fat from coconut oil (Nageswari et al., 1999). Mente et al. (2009) conducted a systematic search of Medline for cohort studies on randomised trials investigating dietary exposures in relation to CHD. They pointed to the moderate evidence of associations that exists for intake of fish, marine n-3 omega PUFAs (Table 2), folate, whole grains, dietary vitamins E and C, beta carotene, alcohol, fruit and fibre.

Although there is important evidence relating to the protective effects of n-3 omega PUFAs on cardiovascular health, very surprisingly, these fatty acids may accelerate heart beat, cause adverse effects and even be life threatening according to the findings of Raith et al. (2005). In their randomised controlled trial involving 200 patients, 1.8 g daily fish oil supplementation caused significantly important accelerations of the heart beat in patients with ventricular tachycardia (VT), an accelerated heart beat initiated within the ventricles that may prevent heart from pumping enough blood and ventricular fibrillation (VF), a heart failure due to sudden cardiac death. The findings are seriously important since it indicates that patients with VF and VT should rather avoid n-3 omega PUFAs. When 37.393 deaths in only USA in 2002 with 1.6% of all deaths that year with $2.2 billion payment to medicare beneficiaries for cardiac dysrhythmias concerned, findings are seriously important and needs further studies for definiteness.

Inuit peoples have a substantially lower rate of acute myocardial infarction, commonly known as a heart attack which occurs when blood supply to heart is interrupted causing some heart cells to die, when compared with Western people despite having a diet high in fats. Studies (Bang et al., 1971; Kromann & Green, 1980) have shown that the diet is high in omega-3 polyunsaturated fats (PUFAs) from sea mammals and fish has a protective effect. In one study, which obtained information on deaths from different diseases for 2005 from US National Center for Health Statistics, Danaei et al. (2009) examined lifestyle and metabolic risk factors in death and determined a deficiency of n-3 omega PUFAs as the eighth highest killer in death for people living in USA. Deficiency of n-3 omega PUFAs with 84 000 death year\(^{-1}\) even beat out nutrition rich in trans fat with 82 000 deaths annually as a causative factor. The same study findings also suggested that the huge number of annual deaths (84 000 year\(^{-1}\)) in USA is mainly depended on deficiency of n-3 Omega PUFAs, EPA/DHA, which can also be prevented by omega 3 supplementation and a change in nutrition style to a diet rich in n-3 omega PUFAs. Thus, the study indicates to the importance of increasing consumer awareness of the dangers of about the drastic deficiency of n-3 omega PUFAs. A recent meta-analysis of randomised controlled studies of omega-3 fatty acid supplementation of the diet by Preiss & Sattar (2009) confirmed that this treatment had a cardiovascular benefit but suggested that more data would be needed to support use in clinical practice. With our present data mentioned above, we can note this cardio protective effect of n-3 omega PUFAs. However according to Lee & Lip (2003), the use of n-3 omega PUFAs should be considered as a part of comprehensive secondary prevention strategy in patients following myocardial infarction. It has also been proposed that ischemia-induced arrhythmias may be prevented by n-3PUFA supplementation (Leaf et al., 2003). In spite of many studies, indicating the protective effect of n-3 omega PUFAs on cardiovascular system, the minimum dose which shows this effect, was not established until the studies by Weber & Raederstorff (2000). They stated that, 1 g day\(^{-1}\) n-3 omega (in the form of fish oil) is sufficient to show this serum triglyceride and LDL lowering effect whilst a daily intake of 3 g of EPA and DHA is regarded as safe by Food and Drug Administration (O'Keefe & Harris, 2000). Similarly, Retterstol et al. (1996) claimed the serum triglyceride and LDL lowering effect of n-3 omega, but as combined with drugs to treat hypercholesterolemia. On the other hand, an insufficiency of n-3 omega PUFAs and high amounts of n-6 omega PUFAs may also increase the atherogenic effects of environmental chemicals such as polychlorinated biphenyls (PCB), leading to dysfunction of the vascular endothelium. In spite of the cardiovascular protective effects of n-3 omega PUFAs, n-6 omega PUFAs do not appear to be correlated with cardiovascular benefits even though they lower LDL and cholesterol (Lecerf, 2009). The effects of LA or PCB are contrary to those of n-3 omega PUFAs, disrupting the endothelial barrier function. Cellular enrichment with LA can amplify PCB induced endothelial cell dysfunction, which brings about a cardio toxic effect (Slim et al., 2001). These findings underline the importance of n-3 omega PUFAs supplementation in daily nutrition in the prevention of diseases associated with high cholesterol levels.

There appears to be significant evidence that n-3 omega PUFAs have a protective effect on the cardio-
vascular system and evidence of an inhibitory effect on inflammation. This evidence made n-3 omega rich foods, especially fish meat, as the most popular meat option when compared with other meats. Among red meat options, beef cut (round) may be advised with a higher α-LN content (32 mg 100 g⁻¹) (as the indicator of n-3 omega PUFAs) and lower palmitic acid content (958 mg 100 g⁻¹) followed by beef cut (leg) with 22 mg 100 g⁻¹ α-LN content and 2804 mg 100 g⁻¹ palmitic acid content and dark chicken meat with 25 mg 100 g⁻¹ α-LN content and 1097 mg 100 g⁻¹ palmitic acid content (Almeida et al., 2006). Linseed oil with 55% LN content may be considered as the optimum plant oil being the richest among others although it is often neglected by the media.

It is possible that the cardioprotective effect of n-3 omega PUFAs is dependent on the anti-inflammatory properties. The anti-inflammatory properties are due to the incorporation of EPA and DHA into cell membranes. NADPH oxidase, the main producer of cell membranes, is also activated by n-3 omega PUFAs. Only after this activation, does the enzyme regulate the cell membrane production and make it more durable and cells become more resistant to extrinsic and intrinsic destructive factors, especially inflammatory agents. This protection against inflammation is of course the same for the cells of blood vessels and the heart (Heine et al., 1999). On the other hand, when omega 3 fatty acids are provided, there is partial replacement of AA in cell membranes by EPA as one of the important members of n-3 omega PUFAs which results in strengthening of the cell (Calder, 2003a,b).

The anti-inflammatory and cardioprotective functions of n-3 omega PUFAs improve the immune system. This improvement which is very important for immune system diseases such as HIV/AIDS, requires nutrients to power the immune system and support maximum cellular protection and function for long term survival. It can be clearly stated that, n-3 omega PUFAs have potential as an immune system defenders and enhancers in immune system deficiencies (Zimmerman, 1997).

n-3 omega PUFAs and diabetes

Diabetes, remarkably increases plasma glucose, fructosamine, triglyceride, LDL and decreases HDL. It also enhances oxidative susceptibility of LDL, catalase activity and NO (nitrous oxide) levels, while increasing the synthesis and release of cytokines (IL-1 and TNF). During the treatment of diabetic rats with n-3 omega PUFAs, a significant decrease of LDL with plasma triglyceride and cytokine synthesis was noted (El-seweidy et al., 2002). One of the very few studies related to the serum glycogen level and n-3 omega intake detected lower glycogen concentrations in n-3 omega fed rats, when compared with casein fed rats (Gavia et al., 2003). The studies of El-seweidy et al. (2002) and Gavia et al. (2003) seem to support the proposal that PUFAs may have a role in the treatment of diabetes because of their availability to lower blood sugar levels and reduce the hazards associated with inflammation. More studies are needed to highlight the sugar lowering effect of n-3 omega PUFAs in human serum profile.

n-3 omega PUFAs are also used for the treatment of diseases in gastrointestinal origin and especially the stimulation of PGE1 secretion by n-3 omega PUFAs by decreasing platelet aggregation (Levy & Herzberg, 1996).

The effect of treatment with n-3 omega PUFAs is closely related to the form of the fatty acid used. Pure EPA supplementation in the ethyl ester form always has a greater effect than fish oil because of the easier absorption of the ethyl ester through the intestinal wall without requiring lipase. As an example, platelet reactivity is more inhibited by pure EPA dietary supplementation than it is, when supplementation is with fish oil extract (Wojenski et al., 1991).

PUFAs and cancer

As with cardiovascular diseases, one initial predisposing factor for cancer appears to be the fat composition of the diet. Whereas an increased ratio of saturated fatty acids in the diet leads to cancer, many researchers have determined the protective effect of dietary eicosapentaenoic acid in diet against cancer in gastrointestinal origin. Increased concentrations of long chain fatty acids and eicosapentaenoic acid (as the main constituents of n-3 omega PUFAs) protect against colorectal cancer (Nkondjock et al., 2003). Dietary supplementation with n-3 omega PUFAs has been shown to produce beneficial effects in patients with pancreatic cancer, by decreasing tumour formation (Gogos et al., 1998) and reducing weight-loss (Barber et al., 1999). Fish oil alone or soy bean and fish oil combined dietary supplementations produced an increase in body weight in a study on rats, indicating their potential for weight gain in cancer (Gavia et al., 2003). n-3 Omega fatty acid supplementation is very effective, not only as an antitumour agent but also in mediating the effects of nutritional interventions by prolonging life span, suppressing autoimmune diseases, decreasing tumourigenesis (Troyer & Fernandes, 1996) and tumour necrosis factor (TNF; a protein which is detected in high concentrations in various types of cancer which increases T suppressor cells) (Simopoulos et al., 1991).

Unlike the significant protective and suppressing effects of n-3 omega PUFAs in cancer and autoimmune diseases, n-6 omega PUFAs increase the risk of tumour promotion, indicating the advantages of olive and canola oils, which are low in n-6 omega (Wood et al., 1996). A 3 g daily supplement of flaxseed, which is a rich...
source of lignan and n-3 omega PUFAs, when combined with dietary fat restriction, results in decreased prostate specific antigen levels and proliferation rate in prostate cancer (Demark-Wahnefried et al., 2001). According to Moyad (2003), one of the initial causes of death in prostate cancer patients is cardiovascular disease rather than cancer. Thus, these patients with prostate cancer should increase their consumption of omega 3 fatty acids as well as maintaining a healthy weight and getting physical activity. The data relating to the protective effect of n-3 omega PUFAs against cancer is mainly determined by the following factors: the type of the cancer, metabolism, genes, sex, age and diet. Whereas n-3 omega PUFAs show their protective effect against cancer on metabolism by acting on the metabolism, high dietary LA (e.g. n-6 omega PUFAs) intake can elevate cancer on metabolism by acting on the metabolism, high dietary LA (e.g. n-6 omega PUFAs) intake can elevate oestrogen levels in pregnancy, altering mammary gland morphology and expression of fat-and/or oestrogen-regulated genes and increasing breast cancer risk (Clarke et al., 1999). Theodoratou et al. (2007) found a significantly important association between n-3 omega PUFAs and colorectal cancer in a large scale meta-analysis, involving data from 1455 patients studied between 1999 and 2006 that, n-3 omega PUFAs decreased the risk of colorectal cancer whilst saturated fatty acids, namely palmitic, stearic and oleic acid increased the risk. Similarly, supplementing the diet of tumour-bearing mice with n-3 omega PUFAs was claimed to slow the growth of cancers including lung, colon, mammary and prostate, according to Hardman (2004). The author also indicates the importance of n-3 omega PUFAs as a complementary medicine which can improve the efficacy of cancer chemotherapy drugs such as doxorubicin, epirubicin, 5-fluorouracil, tamoxifen and of radiation therapy. Geelen et al. (2007), in their meta-analysis, involving fourteen studies, relating to colorectal cancer, suggested an evidence that n-3 omega PUFAs inhibited colorectal carcinogenesis but the authors also concluded that there is insufficient data available to definitively confirm this association.

According to Rose & Connolly (1999), a common feature of most of the mentioned cancer preventive activity of n-3 omega PUFAs is related to the inhibition of eicosanoid production caused by n-6 omega PUFAs. Another suggested effect mechanism of the cancer preventive effect is claimed as the inhibition of transcription activator protein 1 (AP-1), a protein responsible from gene expressions that cause cell proliferation and tumour formation in cancer (Liu et al., 2001).

An important finding which conflicts with findings that claim n-3 omega PUFAs are significantly effective in reducing cancer risk belongs to MacLean et al. (2006). In their review, a total of thirty-eight articles with prospective cohort study design and different levels of exposure in the cohort were included. Interestingly, in their review, a large body of literature, spanning cohorts from many countries, did not provide evidence to suggest a significant association between n-3 omega PUFAs and cancer incidence. According to this meta-analysis in the review, dietary supplementation with n-3 omega PUFAs, as conflicting with many others, is unlikely to prevent cancer.

E. PUFA, brain health and neurological disorders

Phospholipids make up 60% of the dry weight of the brain. An increase in phospholipid concentration of brain cell membranes has a significantly beneficial effect on the treatment of schizophrenia (Horrobin et al., 2002). New pharmacological mechanisms for the treatment of schizophrenia have included omega 3 fatty acids as well as partial dopamine D2-receptor agonism, glutamatergic agents and oestrogen (Fleischhacker, 2003). Phospholipids are also essential for neurone function, especially for synaptic structure and play a key role in the signal transduction responses to dopamine, serotonin, glutamate and acetyl choline. n-3 Omega PUFA s, by controlling the over-activity of T-cells and antiphospholipid antibodies may be effective in decreasing the severity of major depression events (Maes et al., 1993). The same relationship between low numbers of major depression incidents and high levels of omega 3 supplementation has been reviewed by Colin et al. (2003). On the other hand, these inflammatory processes mentioned above, may influence the levels of neurotransmitters, especially by decreasing serotonin levels. n-3 Omega PUFAs, by enhancing the production rate of serotonin, can also reduce the severity of depression (Maes et al., 2007; Song et al., 1998). In cases of depression, there are abnormally low levels of omega 3 PUFAs and EPA whilst excessive amounts of omega 6 PUFAs are seen. The unsaturated fatty acid components of phospholipids are abnormally low in depression, with deficits of eicosapentaenoic acid and other n-3 omega PUFAs and excesses of the n-6 omega PUFA (AA). Despite this, n-3 omega PUFAs can not be administered to the patients as an effective monotherapy to treat depression. However, adjuvant application of folic acid, S-adenosyl-methionine, n-3 omega PUFAs and L-tryptophan with antidepressants may be beneficial, particularly in people with both depression and dietary deficiency (Sarris, 2009). Hamazaki et al. (2005) examined the effect of n-3 omega PUFAs on catecholamines (adrenaline and noradrenaline). In a randomised, placebo controlled double blind study, daily doses of 762 mg EPA + DHA lowered the noradrenaline concentration in blood. Noradrenaline is an important catecholamine which closes vessels and increases blood pressure in many cases of stress and depression. This randomised, placebo controlled, double blind study is the only study, presently, as related to n-3
omega PUFAs and catecholamines. Hallahan et al. (2007) found significantly greater improvements in depression, suicidality and daily stresses by 1.2 g EPA or 0.9 g DHA supplementation as combined with psychiatric care for 12 weeks. Laure & Marc (2006) observed a progressive decline in anxiety as compared with placebo in patients who were given 3 g of EPA and DHA for 3 months as compared with patients receiving a placebo. Similarly, Yehuda et al. (2005) observed reduction of high cortisol levels back to normal values and remediation of sleep disturbances and anxiety during ‘test anxiety’ (an anxiety which may be defined as incapacitating academic syndrome) in students supplied with 225 mg n-3 and n-6 omega PUFAs. Nemet et al. (2006) claimed highly significant therapeutic effects of 1 g day$^{-1}$ supplementation of n-3 omega PUFAs for 16 weeks in children with childhood depression, between the ages of 6–12 years. Similarly, the same dose, 1 g EPA supplementation in twenty-four patients with depression, was claimed as beneficially effective in another double blind, randomised, placebo-controlled study (Frangou et al., 2006). According to a meta-analysis among randomised controlled trials by Freeman et al. (2006), although there is less evidence of benefit in schizophrenia, EPA and DHA may have some potential benefit in major and bipolar depressive disorder but the authors conclude that results remain inconclusive (Freeman et al., 2006).

Frasurer-Smith et al. (2004) examined the relationship between depression and omega 3 and 6 serum levels in patients at the age of 54 years and older in the recovery period from acute coronary syndromes in a case control study. Depressed patients had significantly lower concentrations of total n-3 omega PUFAs and higher ratios of AA to DHA and AA to EPA. They also concluded that their study was a case control study and should have been supplied by both prospective studies and randomised trials.

Antalis et al. (2006) point out that lower levels of long-chain PUFAs, particularly n-3 omega PUFAs in blood have repeatedly been associated with a variety of behavioural disorders including attention-deficit/hyperactivity disorder (ADHD). They reported in their meta-analysis that one small randomised controlled trial with n-3 omega PUFA supplementation in depression in children found a small beneficial effect over placebo. Four placebo controlled trials showed uncertain benefits of n-3 omega PUFAs for children with ADHD while a single placebo controlled trials showed no benefit in autism or bipolar disorder. Reviewers also concluded an absence of studies examining the benefits for first-episode psychosis or schizophrenia in children and adolescents (Clayton et al., 2007). A very high dose, 10 g day$^{-1}$ of EPA was claimed to ameliorate the symptoms of schizophrenia while AA had no similar effect (Peet et al., 1997).

Unfortunately, this study was a small scale study so that two out of the five patients had been taken out of the study due to clinical deterioration. In one of very few studies related to the association of n-3 omega PUFAs and schizophrenia, Fenton et al. (2001) administered 3 g day$^{-1}$ of EPA for 16 week in their double blind, controlled trials, involving eighty-seven patients, but found no difference in improvement in symptoms of schizophrenia and cognitive impairment. Joy et al. (2006) reviewed research findings related to the effects of PUFAs for people with schizophrenia between 1998 and 2002. Limited evidence supports a hypothesis suggesting that schizophrenic symptoms may be the result of altered neuronal membrane and metabolism and neuronal membrane structure and metabolism which are closely dependent on blood plasma levels of n-3 omega PUFAs and their metabolites. The authors of the meta-analysis indicate to the necessity of further large well designed, conducted and reported studies since the results in the field remain inconclusive with very little useful data.

According to Hibbeln (1998), the prevalence of depression is inversely related to the amount of fish consumed. Similarly, other groups have reported a decrease in the ratio of n-3 omega fatty acids to n-6 omega fatty acids in the plasma and erythrocytes of patients with major depression and a decreased n-3 omega fatty acid concentration in erythrocytes with an increased severity of depression (Edwards et al., 1998; Peet et al., 1998). Also, a lower DHA content in mothers milk and lower seafood consumption are associated with higher rates of postpartum depression while omega 3 PUFAs supplementation of the mothers diet improves psychomotor development, cognitive development and birth weight without the risk of negative nitrogen balance which is always caused by n-6 omega PUFAs (Morley, 1998; Hayashi et al., 1999; Woltit et al., 1999; Hibbeln, 2002). Unlike n-3 omega PUFAs, which decrease cytokine production and depression, n-6 omega PUFAs increase cytokine production and therefore, may also directly stimulate depression. However, indirect effects such as the metabolic disorders including cardiovascular diseases, immunological activation, cancer, diabetic complications and osteoporosis may lead to depression or be associated with depression. By protecting against cardiovascular diseases, inflammation, cancer and diabetes, n-3 omega supplementation appears to have the function of reducing the risk and severity of depression both directly and by alleviation of these disorders (Horrobin, 2001). Also, Dyall & Michael-Titus (2008) indicates that increased intake of long chain n-3 omega PUFAs, EPA and DHA may confer benefits in a variety of psychiatric and neurological disorders in neurodegenerative conditions, although the mechanisms underlying these beneficial effects are still poorly understood.
Finally, in the case of AD, various genetic, medical and environmental factors appear to be causative. The risk of AD increases, when one of these factors leads to a decreased cerebral perfusion, which causes an insufficient flow of blood to the brain. Thus, the beneficial effects of n-3 omega PUFAs can decrease the risk of AD by easing the flow of blood in the brain and central nervous system (Heininger, 2000).

n-3 Omega PUFAs and eye health

One of the fields which needs further investigation and evidence as related to the effects of n-3 omega PUFAs is on eye health. One disease of the eye which has been most studied is age related macular degeneration (ARMD), an illness that progressively degenerates the back of the eye (macula). There is also insufficient evidence with few prospective studies and no randomised clinical trials to support n-3 omega PUFAs routine consumption for ARMD prevention (Chong et al., 2008). However, Chiu et al. (2009) claim in their study that weekly consumption of two or three portions of fatty fish can be beneficial for ARMD patients. The claim is based on an 8-year study of 3000 patients who were given n-3 omega supplements and monitored for the possible development of macular degeneration. Findings determined ARMD 25% less likely among participants consuming a diet rich in omega 3 fatty acids, EPA and DHA. The authors concluded that the combined consumption of a diet rich in omega 3 with low glycemic index carbohydrates such as whole bread products rather than processed may diminish the risk of progression of the disease to the advanced state. Deficiency of n-3 omega PUFAs was also shown to be adversely effective especially on visual and neural function in preterm infants which may need to be supported by n-3 omega formulas since n-3 omega PUFAs rich formula supports for visual and cortical function significantly in such infants (Hoffman et al., 1993).

Causes of ARMD have still not been identified although any arterial plaque may also affect the delicate blood vessels in the eye. Because of such possibility, it is commonly believed that a low-fat diet, but rich in n-3 omega PUFAs could help to guard against ARMD. In one of the studies, testing this theory, 90 000 participants over the age of 50 years, were monitored over a 12-year period. Findings of the research claimed that high intakes of LA (n-6 omega PUFA), exist in beef, pork and lamb and high amounts and trans fat in margarine appeared to increase the risk of ARMD, while the participants who consumed n-3 omega PUFAs rich foods such as tuna were about 35% less likely to develop ARMD (Cho et al., 2001). Ouchi et al. (2002) evaluated the relationship between fatty acids and ARMD by comparing the fatty acid fractions within the red blood cell membrane and plasma of 11 ARMD patients and ten healthy individuals (controls). They determined that there was a higher AA and DHA in the controls than in the ARMD patients which indicates that PUFAs, vulnerable to free radicals and reactive oxygen species, easily peroxidised, may be related to ARMD induction. Another study that claims the beneficial effects of n-3 omega PUFAs on eye health was conducted by Seddon et al. (2001). In the case study with 349 individuals at the age of 55–80 years, a higher intake of vegetable, monounsaturated and polyunsaturated fats and linoleic acid (n-6 omega PUFA) in 8 years was claimed to be associated with a greater risk for advanced ARMD while diets high in n-3 omega PUFAs and fish were inversely associated with risk for ARMD when intake of LA was low. Opposite to the findings of mentioned studies which indicates to the beneficial effects of n-3 omega PUFAs on ARMD, any significant relationship between age-related maculopathy and dietary fat including n-3 omega was not detected in a large cross-sectional survey of 7883 participants aged between 40 to 79 (Heuberger et al., 2001). Confirming this, oral n-3 omega PUFA supplementation as 1000 mg day\(^{-1}\) did not make any effect on improving visual activity recovery time. The authors underlined the importance of combined use of n-3 omega PUFAs with photodynamic therapy for ARMD in order to improve retinal metabolic function only under this combined use up to an extent (Scorolli et al., 2002). Since n-3 omega PUFAs exert important effects on eicosanoid metabolism, membrane properties and gene expression, it is reasonable to hypothesise that maternal n-3 fatty acid intakes might have significant effects on infant visual function and neurodevelopmental status. There is also very limited data as related to the effects of n-3 omega rich nutrition and supplementation during postpartum period on visual acuity of infants. In one of these studies, 1.3 g n-3 omega PUFAs supplementation of lactating women for the first 4 months of postpartum also did not effect visual acuity of infants (Lauritzen et al., 2004). Similarly, DHA in algae origin, but with a lower dose (200 mg daily), was given to lactating women during the first 4 months of postpartum. It had no effect on either neurodevelopmental progress of the infants at 12 months of age 4 years or the visual function at 4 or 8 months of age (Jensen et al., 2005). Confirming these earlier findings, Gibson et al. (1997) claimed that, 200, 90 and 130 mg day\(^{-1}\) DHA supplementation of breast feeding women during the first 12 week of postpartum period did not effect visual acuity of the infants. No clear consensus exists in studies as related to the effects of n-3 omega PUFAs on infant visual function and neurodevelopmental status of infants while only a few available data suggest a modest effect (Jensen, 2006).

Findings clearly indicate that a definite effect of n-3 omega PUFAs on eye health can not be claimed because
some of the findings, especially those based on findings of meta-analysis are conflicted while some of the researches needs further evidence of more prospective studies and randomised clinical trials in ‘n-3 omega and eye health relation’.

**Current status of n-3 omega PUFAs**

**Questions still waiting to be highlighted**

In addition to their reputed beneficial effects supported by strong scientific evidence (Davidson & Geohas, 2003), omega 3 PUFAs have one notable adverse side effect, they stimulate oxidation (Nardini et al., 1995) which necessitates the regular use of an antioxidant, commonly Vitamin E (Arkhipenko & Szantova, 1995; Linseisen et al., 2000; Gil, 2002) in combination with n-3 omega PUFAs. Using such an antioxidant, can easily lower the excessive oxidation rate, induced by these fatty acids (Puiggros et al., 2002). The conjoint use of n-3 omega PUFAs and vitamin E (α-tocopherol) after surgery in the stomach, intestines and digestive organs, protects patients against inflammation in the postoperative period, without increasing lipid peroxidation (Linseisen et al., 2000).

Despite the substantial amount of knowledge related to the anti-inflammatory and sleep promoting effects of n-3 omega PUFAs, the minimum effective doses have not been sufficiently determined. Establishing such correct doses will require a considerable amount of time and research, due to the spontaneous metabolic conversion of omega 3 and omega 6 fatty acid into each other and the differences in each persons unique serum omega profiles.

The potential of PUFAs to increase energy utilisation has not yet been clearly demonstrated due to a lack of studies related to their use as energisers in sports and postoperative periods (Emmanuel & Hubbard, 1993). Oxygen free radicals (OFR) are very effective in the development of hypercholesterolemic atherosclerosis, resulting due to excessive cholesterol on the inner layer of blood vessels. IL-1, LTβ and TNF are the end products of PGE2 metabolism which stimulate polymorphonuclear leucocytes and monocytes to produce OFR (Fig. 1). The n-3 omega PUFAs reduce the rate of production of OFR by inhibiting the production of IL-1, LTβ and TNF (Prasad, 1997). However, they are also highly susceptible to the oxidation themselves. Thus, the long-term treatment at a high dose (7.7 g day⁻¹) with these fatty acids also causes an increase in lipid peroxidation. Therefore, the risk of this oxidation on plasmic membranes of red blood cells should be considered as a serious side effect in nutrition with n-3 omega PUFAs (Bartoli et al., 1995). Similarly, incorporation of long-chain n-3 omega PUFAs in LDL, results in a decrease in its resistance of LDL to oxidation because of the high degree of unsaturation of these fatty acids. A study conducted on rats, indicated a decrease in plasma antioxidant potential and an increase in the susceptibility of LDL to oxidation (Nardini, 1995). In contrast, Brude et al. (1997) found no difference in LDL particle susceptibility to oxidation between a group receiving n-3 omega supplement and a group receiving a placebo.

Another major problem when employing n-3 omega PUFAs in the food industry is the risk of oxidation in meat products enriched with n-3 omega PUFAs. O’Keefe et al. (1995) showed that, in meat of poultry which were fed with 8% and 12% fishmeal, high levels of peroxide developed during refrigeration. Similarly, supplementation of the diet with fish oil (as n-3 omega source) was not effective on colour retention and oxidative stability of lamb during refrigeration, according to Ponnampalam et al. (2001). These results seem to be far from highlighting oxidative stress due to n-3 omega supplementation of the foods but what we definitely know is the necessity to use n-3 omega PUFAs as combined with fat soluble antioxidants, not only in human metabolism but also in meat and meat products. These results have shown that the PUFAs should be combined with antioxidants to achieve their protective effects. Given the apparent importance of these PUFAs to human health, it is hoped that meat producers and meat scientists will develop methods for including omega 3 in meat, meat products and animal feed possibly via feeding regimes including appropriate antioxidant support. Otherwise, omega 3 use in meat industry without antioxidant addition may result in oxidation and discolouration of meat rather than an increase in meat quality.

Contrary to preconceived opinions, EPA and DHA (as the precursors of n-3 omegas) have no significant relevance in the evaluation of the omega quality of fish and marine products, since AA and EPA, DHA, LN can be converted into each other. Therefore, when evaluating the nutritional quality of foods, the ratio of total fat content to the amount of EPA and DHA should be considered rather than the content of DHA and EPA, separately. This ratio should be as small as possible, as in halibut, cod, haddock and tuna. α-LN and AA do not mean anything by themselves, since they can be readily converted into each other. The ratio of total fat content to the total amount of α-LN may also be considered as the main criterion in determining the omega quality of oils.

**Areas of future research**

Whilst the beneficial effects of n-3 omega PUFAs on metabolism such as reducing the risk of cancer, cardiovascular diseases (esp. atherosclerosis), many inflammatory disorders (such as ulcerative colitis, Crohn’s disease
and asthma), diabetes, depression and even AD have been indicated, the effective doses for each of these diseases and individual patient requirements still wait to be determined.

Although we have got important scientific evidence and data as related to the protective effects of n-3 omega PUFAs in cardiovascular health and cancer, we still do not know the mechanism of these effects. Further studies are needed to investigate these mechanisms.

Another important question which is requiring investigation appears as the antagonism of dietary fibre and omega 3 fatty acids in some omega 3 rich food products. Flax seed, purple grape seed, canola seed with many others, are used by many people as omega 3 supplements in many countries. But, ‘should we trust to the omega 3 contents of these food supplements since they also contain high amounts of dietary fibre, such as lignan, which can bind some omega 3 fatty acids and decreases their bioavailability?’ is another question to be highlighted. Studies are needed to determine which fibres bind which omega 3 PUFA and the relevance of these interactions in each product or food material. Otherwise, many people in the world will continue to use these interactions in each product or food material. Otherwise, many people in the world will continue to use omega 3 from these types of supplements despite the fact that, these fatty acids are bound to the fibre and therefore excreted directly without being absorbed by body and hence without effect.

Some studies used to administer very high doses of n-3 omega PUFAs, like 10 g day\(^{-1}\) and 6.6 g day\(^{-1}\) administrations by Peet et al. (1997) and Su et al. (2003). Both studies claimed beneficial effects of these megadoses on depression and schizophrenia. However the risk about internal bleeding risk due to the anticlotting effect of n-3 omega needs to be considered when administering large megadoses. The findings will no more be important, no matter how they claim beneficial effects, as long as the risk of internal bleeding in the administration of megadoses is always possible. This important point should always be taken into consideration in further studies.

Suzuki et al. (2004) examined the association between daily intake of n-3 omega PUFAs and depression in Japanese cancer patients. In this big scale study (with 771 patients), their findings indicated that there was no association between EPA and DHA intake. The research raises a question which needs further studies to be highlighted, ‘which one has got stronger association with cancer; \(\alpha\)-LN intake or EPA and DHA intake?’. Confirmatory studies are needed.

Another question we face with omega 3 seems to be the reliability and the sensitivity of some of the mentioned and other research as related to omega 3. In many instances, the authors indicate the necessity to use conditional statements rather than definite expressions when discussing and evaluating n-3 omega studies. For example, how can we trust definitely and completely to the use of terms such as ‘Western style’ or ‘Far East style’ nutrition when there may be a significant dietary personal variations which use lower or higher amounts of n-3 omega. In other words, variations in exposure at the population level do not always correspond to variations among individuals within any given population. Therefore, we should note that, we need case controlled studies rather than cohort studies or cohort-controlled studies that should compare individuals with high and low consumption within populations. Also, like western style and east style nutrition, term ‘fish oil’ seems insufficiently specific and clear since EPA and DHA (n-3 omega in fish oil) vary between fish species although high concentrations are found in cold water species such as salmon, mackerel, herring and sardines, whilst only low concentrations are found in lean fish such as sole, cod and halibut. Similarly, whiting deposits most of its n-3 omega content into its abdominal cavity and naturally loses this content during evisceration prior to cooking. Therefore, in order to conduct an accurate evaluation of the effects, we need to know fish species, fish oil type and the person, with his/her exact daily nutrition profile. In the evaluation and consideration of new future studies as related to n-3 omega fatty acids and their beneficial effects, rather than general terms such as African or western style or fish oil, the mentioned approach may increase the sensitivity and reliability of the research on n-3 omega. Otherwise, there will still be conflicting reports or studies with poor sensitivity and there will have to use of possibility terms rather than definite expressions about the beneficial effects of dietary supplementation with n-3 omega fatty acids.

What is the situation in relation to the side effects of n-3 omega PUFAs such as fattening of mucosa, the risk of internal bleeding or their unfavourable interaction with other food ingredients? Despite the lack of knowledge in relation to adverse effects, omega 3 supplements are still being used without control in an attempt to decrease the mortality rate associated with certain diseases. Clinically, this often leads to serious side effects such as bleeding from an excessive intake of n-3 omega or thrombosis and emboli from an excessive intake of n-6 omega fatty acids.

Conversely, the studies of O’Keefe et al. (1995) and Ponnampalam et al. (2001) showed either high peroxide or no change in peroxide respectively, following omega 3 supplemented feeding of poultry and mutton which conflict with other studies showing the antioxidant effects of omega 3 fatty acids. Thus, it is unclear whether n-3 omega PUFAs are oxidants increasing peroxide in meat products or antioxidants.

### Promising n-3 Omega PUFA supplies for future

The primary sources of n-3 omega, are some algae and fungi from the order Mucorales (Bajpai & Bajpai, 1993),...
Ooligan grease (Thaleichthys pacificus) (Kuhnlein et al., 1996), Camelina sativa L. Crantz seed (Rokka et al., 2002) and sea/fresh water fish, vegetable and oil products (Sauci et al., 1994). Recently, interesting and promising studies have succeeded in extracting high EPA levels from diatoms such as Phaeodactylum tricornutum which seems less expensive than from cod liver (Lebeau & Robert, 2003). Similarly, DHA-rich oil content from microalgae, Ulkenia sp., improved some CHD risk factors, resulting in lower TG:HDL cholesterol and plasma TG but increased LDL cholesterol (Geppert, 2006). Unfortunately, these studies are also very few with a very limited scientific evidence and data.

**Future research required**

When all the above-mentioned studies are considered, it is possible to say that n-3 omega PUFAs are clearly beneficial food supplements, especially with their protective effect on cardiovascular system.

Most of the patients, who are receiving treatment in cardiology and neurology clinics in the USA, are given an anticoagulant, in combination with a weekly diet programme. The dietary program is used to counteract the dosing inadequacies related to the anticoagulant. Thus, the prothrombin (Ptz) time (a criteria for determining the clotting level of blood) is monitored and when there is an excessive anti-clotting due to an overdose of the anticoagulant, the diet is changed to one, low in omega 3 whilst, in cases of anticoagulant insufficiency which results in high levels of coagulation in the blood as confirmed by a short Ptz time, the diet is changed to one, rich in omega 3. Unfortunately, this approach is not being adopted in the hospitals of most European, Middle East, Asia and Far Eastern countries. Research supporting this treatment is needed to encourage its more extensive use.

According to FAO/WHO, the recommended dose of essential PUFAs in a healthy diet in daily nutrition is 5–10:1 (n-6:n-3) (Trautwein, 2001), but this dose was not established on the basis of different serum DHA and EPA levels and the effect of the dose on these levels. Interestingly, 5–10:1 (n-6:n-3) intakes, recommended by FAO/WHO, have been proven to have adverse effects on metabolism (Simopoulos, 2002b). Further, there is no study about serious side effects (such as internal bleeding) that arise from an excessive intake of n-3 omega PUFAs. Thus, more information relating to the appropriate intake levels is needed.

Although there is no doubt of their beneficial effects, indeed, they might even be considered an essential to be one of the basic nutritional components of daily nutrition. However, their efficacy is dependent upon the ratio of n-6:n-3 and the condition being treated. It has been established that, only lower ratios between 2.5:1(n-6:n-3) and 5:1(n-6:n-3) are beneficial while a daily intake of 2.5:1(n-6:n-3) has been proven to act beneficially in cases of colorectal cancer, 2–3:1(n-6:n-3) on rheumatoid arthritis, and 5:1(n-6:n-3) on asthma (Simopoulos, 2008). Interestingly, 5–10:1 (n-6:n-3) intakes, recommended by FAO/WHO, have been proven to have adverse effects on metabolism (Simopoulos, 2002b). The recommended average daily n-3 omega PUF intake was recommended to be increased from 0.1 to 0.2 g day$^{-1}$ by the UK dietary guidelines while it was recommended as above 0.2 g day$^{-1}$ by Committee on Medical Aspects of Food Policy (COMA) that the current UK recommendation for the intake of n-3 omega PUFAs seem to need to be revisited (Ruxton et al., 2007). American Heart Association (Lichtenstein et al., 2006) and The American Dietetic Associations of Canada (Kris-Etherton & Innis, 2007) recommend daily intakes of EPA and DHA as 0.5–1.0 g. Institutes of Medicine (xxx, 2002–2005) recommends as 0.11–0.16 g and The American Dietetic Associations of Canada (Kris-Etherton & Innis, 2007) recommends the same amount with American Heart Association as 0.5 g.

Additionally, the recommended daily intakes, in cancer, diabetes, ulcerative colitis, Crohn’s disease, asthma, depression and AD, have yet to be determined and thus represent an important area for future study. Thus, studies to define the recommended dose are still needed.

Catecholamines (adrenaline and noradrenaline) play an important role in stress and depression by constricting and dilating blood vessels. We have got no data, except only Hamazaki et al. (2005) who have mentioned the importance of PUFAs in relation to brain health and neurological disorders. So, the association between n-3 omega PUFAs and catecholamine metabolism needs further studies to be highlighted. Also, in spite of a limited data and evidence about the association between n-3 omega PUFAs and schizophrenia and, the potential effects of the fatty acids in schizophrenia remains completely unclear with many questions waiting to be answered.

One of the missing field about n-3 omega PUFAs which should be studied, is the effect on quality of pregnancy although a randomised, double-blind, placebo controlled study in UK in 113 high risk pregnancy showed no evidence for any useful effect of 1.62 g EPA and 1.08 g DHA supplementation for women at high risk of adverse outcomes from pregnancy during 38 weeks of gestation (Onwude et al., 1995). Rump et al. (2001) examined the relation between cord plasma essential fatty acid composition and birth weight and indicated a positive relation of dihomo $\alpha$-LN concentration to birth weight scores in spite of a negative relation of both AA and DHA. In spite of the association between dihomo $\alpha$-LN concentration and birth weight, there is not any study yet, to highlight the
effects of n-3 omega rich consumption during pregnancy on birth weight.

Allograft coronary arteriosclerosis, hardening of the arteries followed by organ transplantation is a common problem in cardiology. Sarris et al. (1989) administered 3 mg kg\(^{-1}\) day\(^{-1}\) fish oil to rats for 11 days, followed by heart allograft. Their findings demonstrated that fish oil supplementation inhibited accelerated coronary arteriosclerosis in heart allograft immunosuppression. But, the material in the study is animal. Additionally, 3 mg kg\(^{-1}\) day\(^{-1}\) dose is a mega dose which may cause side effects such as an increased risk of internal bleeding in the case of their long-term use. Also, the long-term use of them without an antioxidant can trigger oxidation and free toxic peroxy radical production. The use of lower doses as combined with an appropriate antioxidant to ameliorate allograft coronary arteriosclerosis in man should be investigated with further studies.

The very limited number of studies as related to the new n-3 omega sources such as algae and the effects of n-3 Omega PUFAs, DHA and EPA, in microalage origin, requires further investigation. Such biotechnology studies are urgently needed to create diets rich in n-3 omega by using rich omega 3 fatty acid contents of these types of micro-organisms.

Unfortunately, there seems to be no study related to the effects of n-3 omega intake on bone and skeletal health. Only one study, on rats, carried out byhirois et al. (2003), showed that feeding fish oil to males had no effect on the biochemical strength of femurs and vertebrae as measured by three point bending and compression whilst females fed the same fish oil diet had reduced growth in length and a lower vertebral peak load. More investigation is required to highlight the effects of n-3 omega PUFAs on human bone strength and susceptibility to fractures.

In spite of some available data and evidence about association between n-3 omega PUFAs and depression, anxiety and schizophrenia, we have got very few data as related to the association between n-3 omega PUFAs and dementia. According to the findings ofCherubini et al. (2007), people with dementia have significantly lower levels of n-3 omega PUFAs in their blood than people at the same age with normal cognitive function while there was no relation between dietary intake of n-3 and n-6 omega and dementia in the study of Devore et al. (2009). More future studies are required to highlight the association between dementia and n-3 omega PUFAs. However, most of the limited evidence and data about the relationship between of n-3 omega PUFAs and dementia claims no association between them. Kröger et al. (2009) evaluated the association of erythrocyte membranes, total n-3 omega PUFAs; EPA and DHA and blood mercury with the incidence of dementia and AD. The study involved 514 patients with dementia at the age of 65 and older between 1991 and 2002, but no associations between n-3 omega PUFAs and dementia or AD were found. In another study about the association of n-3 omega PUFAs with dementia, 5395 participants at the age of 55 years and older, were investigated. But, similarly, the findings did not indicate to any association of typical fish intake in high amounts for 9.6 years with dementia or AD.

A possible explanation for these negative results relates to the ease of oxidation of PUFAs. ApoE4 (Apolipoprotein E4) is a protein which is produced and inherited under the control of E4 gene. The protein attaches itself to a particular receptor on the surface of brain cells. The receptor adheres to the protein which is called amyloid precursor protein. The brain cells transport this protein mass inside and it is attacked by proteases in the cell. The fragments which are produced by the attack are believed to cause the cell death in brain tissue. In their review, Cole et al. (2009) indicate that, high oxidative stress due to the higher concentrations of ApoE4 in very late stages of dementia and AD, limits the efficacy of n-3 omega PUFAs on dementia and AD. Another limitation is because dementia risk doubles with every 5 years over age 65 years. Therefore, the initial protective effect of the fatty acids against dementia and AD may be due to their protective effects against cardiovascular diseases rather than their direct effect. Cole et al. (2009) included that a direct association of n-3 omega PUFAs with dementia and AD can not be claimed definitely, since most of the studies are case control, small scale experiments but not randomised and large big scale studies.

It has been proposed that, the meat industry should enrich their meat products with these fatty acids. The enrichment is achieved by feeding animals with appropriate diets enriched with n-3 omega PUFAs. In one of these studies, linseed oil, forages (rich in LN) and fish meal were used as the feed ingredients for beef, mutton and pork, prior to the slaughter (Raes et al., 2003). However, there have been no studies on serum cholesterol and n-3 omega levels of meats followed by consumption of these n-3 omega enriched diets in the period before slaughter. After such studies have been carried out, n-3 omega PUFAs might become the basic anticholesterolomic additives of the meat industry.

It has been suggested by Levy & Herzberg (1996) that omega 3 supplementation inhibits platelet aggregation and therefore the same supplementation may ease bile flow and therefore assist in the treatment of renal failure. n-3 Omega may be used as a dietary measure like statins, L-carnitin and bicarbonate in the treatment of patients with chronic haemodialysis because of their LDL lowering potential (Kovacic et al., 2003). Further research is required in the field of nephrology to confirm these findings.
Conclusion

Presently, there is an important amount of scientific data as related to the beneficial and protective effects of n-3 omega PUFAs and their effects against inflammation, cancer and heart diseases. The association between major and bipolar depression, schizophrenia, pregnancy quality, osteoporosis, renal failure and n-3 omega PUFAs still requires further studies to be highlighted. Some algae species and dinoflagellates appear as potentially rich sources of n-3 omega PUFAs for the very near future although we have also got very limited number of researches in the related area. The greater effects of mega doses in some diseases have been advocated but the risk of side effects such as internal bleeding associated with such doses was neglected like the negligence of antioxidant administrations in many studies which should be combined with n-3 omega administration.

The effect mechanism of n-3 omega PUFAs on catecholamine metabolism, the daily recommended intakes for cancer, heart disease and diabet suffered patients, pregnant women, the elderly and children, the type of n-3 omega PUFAs – LN, DHA or EPA or both, the stronger effect, possible serious side effects of n-3 omega PUFAs on patients with ventricular tachycardia and ventricular fibrillation and finally, the potential of n-3 omega PUFAs to ameliorate coronary atherosclerosis after heart transplants are all the initial questions which still wait to be studied and answered.

More studies are needed to define the status of n-3 omega PUFAs in food and nutrition science. The studies required to be performed in a very near future should rather be double blind, placebo controlled, large big scale, randomised and cohort prospective studies rather than case control in small scale.

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