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Omega-3 fatty acid: Living longer happier from complexities

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ABSTRACT

Lipids are important nutrients, providing 25-45% of dietary energy in most affluent societies, whereas certain isolated low-technology populations may consume as little as 9-12% of energy as lipids. Lipids are important for use, storage and transport of energy, for insulation (thermal and electrical) and for mechanical protection. In addition, lipids provide polyunsaturated fatty acids (PUFA) that are essential nutrients of importance for several cellular functions in the body including ligands for transcription factors, precursors of signal molecules and building blocks in all cells of the body. It is well known that a given type of nutrients may have several biological effects. Many nutritional factors play important roles in the development of several diseases. Coronary heart diseases, stroke, high blood pressure, overweight, gallstone, several types of cancer, some types of birth defects and inflammatory diseases, are all related to dietary factors. Excess intake of saturated fat, trans fat and cholesterol represent the most well established dietary risk factors for development of cardiovascular diseases , where as very long-chain omega-3 fatty acids and monounsaturated fatty acids may provide beneficial effects. Omega-3 fatty acids and they have been important ingredients of the human diet for many populations during thousands of years. In addition, several thousand studies of epidemiological as well as experimental types have been performed for improving the status of human health.

KEYWORDS: *Lipids, polyunsaturated fatty acids, transcription factors, dietary factors, omega-3 fatty acids.*

1. INTRODUCTION:

Lipids are important nutrients, providing 25-45% of dietary energy in most affluent societies, whereas certain isolated low-technology populations may consume as little as 9-12% of energy as lipids [1, 2]. Lipids are important for use, storage and transport of energy, for insulation (thermal and electrical) and for mechanical protection. In addition, lipids provide polyunsaturated fatty acids (PUFA) that are essential nutrients of importance for several cellular functions in the body[3-5] including ligands for transcription factors, precursors of signal molecules and building blocks in all cells of the body. It is well known that a given type of nutrients may have several biological effects.

Omega-3 fatty acids are long chain, polyunsaturated fatty acids (PUFA) of plant and marine origin. Because these essential fatty acids (EFAs) cannot be synthesized in the human body, they must be derived from dietary sources. Flaxseed, hemp, canola, and walnuts are generally rich sources of the omega-3 PUFA alpha-linolenic acid (ALA). Fish provide varying amounts of omega-3 fatty acids in the form of docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA). ALA can be metabolized into the longer chain EPA and DHA.

The role played by EFAs in the human body has been the subject of volumes of international research, particularly in recent years. The results indicate that omega-3 fatty acids may be of value in the treatment of various medical conditions. The brain contains a high concentration of PUFA (approximately 20 percent of dry weight) and, in the nervous system, one out of every three fatty acids (FAs) belong to the PUFA group. [3, 4] Given the high concentration of EFAs in the nervous system, it is not surprising that investigators have focused on the role of omega-3 fatty acids in brain function. Recent research underscores the important role of these fatty acids in central nervous system (CNS) function, and the potential EFAs have in the treatment of various neuropsychiatric disorders. While beneficial effects of omega-3 fatty acids have been linked to Alzheimer's disease, attention deficit hyperactivity disorder, autism, schizophrenia, hostility, anxiety,

and bipolar disorder, the focus of this article will be the role of omega-3 fatty acids in the neurobiology and treatment of major depressive disorder.

Many nutritional factors play important roles in the development of several diseases. Coronary heart diseases, stroke, high blood pressure, overweight, gallstone, several types of cancer, some types of birth defects and inflammatory diseases, are all related to dietary factors. Excess intake of saturated fat, trans fat and cholesterol represent the most well established dietary risk factors for development of cardiovascular diseases [6], where as very long-chain omega-3 fatty acids and monounsaturated fatty acids may provide beneficial effects [7-9]. Fish and other marine animals, and oils from these sources are rich in omega-3 fatty acids, and they have been important ingredients of the human diet for many populations during thousands of years. In addition, several thousand studies of epidemiological as well as experimen- tal types have been performed using cod liver oil or fish oil, mostly demonstrating beneficial effects on health. These facts provide good evidence that dietary intake of omega-3 fatty acids from marine animals is healthy as well as very safe. Although concern about pollutants in food products of marine origin has been expressed, there seem to be markedly more advantages than harmful effects of consuming marine foods. This is probably due to the health effects of omega-3 fatty acids themselves, in addition to the positive effects promoted by replacing unhealthy nutrients like hard fat with marine fat.

2. FOOD SOURCES OF OMEGA-3 FATTY ACIDS

ALA is found in plants, animals, plankton and marine species. Up to 80% of the fatty acids in leafy green plants is in the form of ALA; but because their overall fat content is low, leafy plants do not contribute significant amounts of ALA to our diets . Flax is the richest source of ALA in the North American diet. ALA is also found in walnut oil, canola oil, olive oil, and soybean oil; in nuts such as butternuts and walnuts; in soybeans and pumpkin seeds; in omega-3- enriched eggs; and in purslane. Fish contain only trace amounts of ALA, although some species of fish, particularly fatty marine fish such as salmon, mackerel and herring, are rich in EPA and DHA. EPA and DHA are found mainly in fatty fish such as mackerel, salmon, tuna, herring, lake trout and anchovy. Other sources include fish oil capsules; marine algae, which are rich in DHA but contain negligible amounts of the other omega-3 fatty acids ; and omega-3-enriched eggs derived from laying hens fed a ration containing either microalgae, which increase the DHA content of the yolk , or flax, which increases the ALA, DPA and DHA content of the yolk .

In most modern societies the quantitatively most important source of omega-3 fatty acids is derived from α-linolenic acid (ALA, C18:3 omega-3, also designated 18:3n-3) found mostly in vegetable oils. Linseed oil, canola oil and soybean oil contain approximately 57%, 8% and 7% α-linolenic acid, respectively, but these oils are without any eicosapentaenoic acid (EPA, C20:5n-3) or docosahexaenoic acid (DHA, 22:6n-3) . Significant amounts of very long-chain omega-3 fatty acids are obtained from fatty fish (herring, mackerel, salmon, trout, eel, anchovies, sardines, etc), in addition to fish oil, cod liver oil, tuna fish oil and krill oil . The fattier the fish is, the more EPA and DHA it will contain. The ratio of these two fatty acids will, however, differ between the species of fish (10). The omega-3 fatty acids in fatty fish or cod liver are not synthesized in the fish itself but in very small organisms called phytoplankton before the marine fatty acids are transferred through the food chain to the respective fishes, seals and whales. A traditionally important and widely used source of very long-chain omega-3 fatty acids in some (Nordic) countries is cod liver oil, whereas fish oil is used widely in many countries. Krill has recently come into focus as a large source of marine oil in which the substantial proportion of the fatty acids are bound in phospholipids, representing approximately 45% of the total fatty acids present. In most other marine oils the majority of omega-3 fatty acids are found in triglycerides.

The dietary intake of α-linolenic acid ranges between 1 and 2 g/ day in most populations where vegetable oils are in common use, whereas the intake of very long-chain omega-3 fatty acids varies between 0 and 14 g/day [11,12]. True vegetarians and vegans consume just tiny

amounts of the very long-chain omega-3 fatty acids, whereas traditional Greenland Intuits have been reported to eat more than 14 g/day [12]

3. CHEMISTRY AND ORIGIN

Fatty acids are hydrocarbon-chains with a methyl group in one end of the molecule (termed omega = ω or n) and an acid group (often called carboxylic acid) in the other end. There are two major nomenclatures of fatty acids. In the most commonly used nomenclature the carbon atom next to the carboxyl group is called the Alfa-carbon (α-carbon) with the consecutive carbons named β-carbon etc. The letter n is often used instead of the Greek ω to describe the methyl end. Furthermore, it is quite common to use the systematic nomenclature for fatty acids where the locations of double bonds are indicated with reference to the carboxyl group.

Nomenclature for fatty acids

$CH_3 - (CH_2)_n - CH_2 - CH_2 - COOH$

ω β α

The structures of different types of fatty acids. Saturated fatty acids are "filled" (saturated) with hydrogen. Monounsaturated fatty acids have one double bond in different positions from the ω-end. In PUFAs the first double bond may be between the 3rd and the 4th carbon atom from the ω carbon, and these are called omega-3 fatty acids. If the first double bond is between the 6th and 7th carbon atom counted from the methyl end, they are called omga-6 fatty acids. The body is unable to introduce double bonds between position 7 and the ω end of the molecule. PUFAs are produced only by plants and phytoplankton's, and are therefore essential to all higher organisms, including fish and mammals. Omega-3 and omega-6 fatty acids cannot be interconverted; therefore both these classes of fatty acids are required in the diet [11]. Omega-3 and omega-6 fatty acids are chain-elongated and desaturated in the body. Retro conversion of DHA to EPA often takes place and can thereby provide an important precursor for eicosanoids like prostaglandins, thromboxanes, leukotrienes and hydroxy-fatty acids, although the retro conversion is relatively limited in man [13]. Retro conversion is a paroxysmal reaction, involving one cycle of β-oxidation with some auxiliary enzymes [14].

ALA can be chain-elongated, desaturated and converted to EPA, and thereafter to DHA in higher organisms like mammals. In adults this conversion is efficient enough to provide sufficient EPA and DHA to avoid any symptoms of omega-3 fatty acid deficiency, but in the fetus and in premature and newborn infants, DHA as well as arachidonic acid (AA, 20:4n 6) are both essential [15].

3.1 Metabolism

Metabolic Pathway of Dietary Omega-3 Fatty Acids

Alpha-linolenic acid (ALA 18:3n-3)

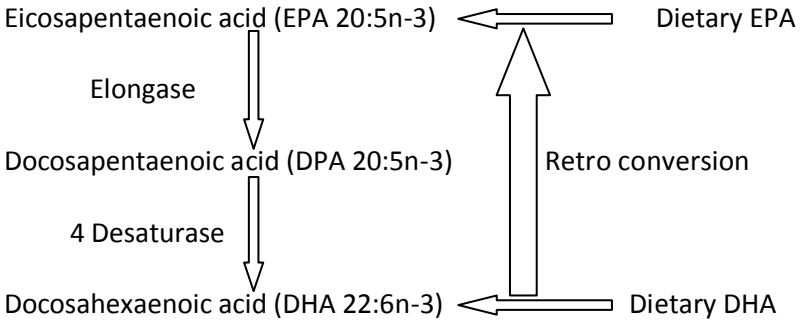
6 Desaturase ⇩

Stearidonic acid (SDA 18:4n-3)

Elongase ⇩

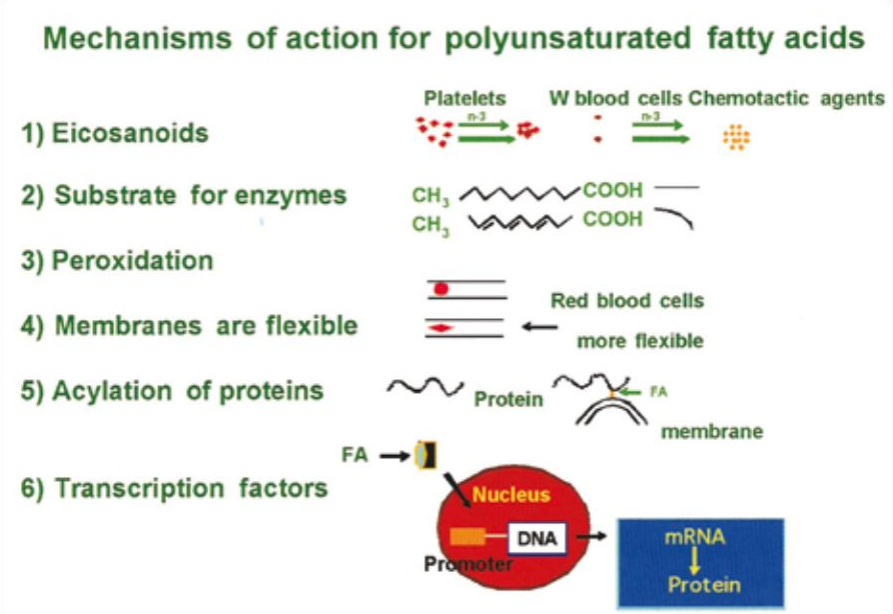
Eicosatetraenoic acid (ETA 20:4n-3)

5 Desaturase ⇩



4. MECHANISMS OF ACTION OF OMEGA- 3 FATTY ACIDS

The different mechanisms by which omega-3 fatty acids can influence biological systems and thereby health, are:



4.1 Eicosanoids

Eikosa means 20 in Greek and refers to the number of carbon atoms in the PUFA from which the eicosanoids are formed. Eicosanoids are important signal molecules [11, 16] including leukotrienes, prostaglandins, thromboxanes, prostacyclins, lipoxins and hydroxy-fatty acids. In addition, two new families of lipid mediators have been discovered, resolvins (resolution phase interaction products) and protectins, both derived from omega-3 PUFA [17].

These have potent anti-inflammatory, neuroprotective and pro-resolving properties. EPA-derived mediators are named resolvins of the E series (RvEs), and those synthesized from DHA are resolvins of the D series (RvDs) and protectins. Eicosanoids are important for several cellular functions like platelet agreeability, chemotaxis (movement of blood cells) and cell growth. Thus, eicosanoids influence homeostasis, inflammation and cell differentiation including cancer.

4.2 Substrate specificity

Omega-3 fatty acids may execute their action by having a different ability to interact with enzymes compared to other fatty acids. For example EPA is a poorer substrate than all other fatty acids for esterification to cholesterol [18] and diacylglycerol [19].

For other enzymes, omega-3 fatty acids are the preferred substrate[20], leading to preferential incorporation of omega-3 fatty acids into some phospholipids. Altered substrate specificity of omega-3 fatty acids for acyl-CoA:cholesterol

acyltransferase (ACAT) and acyl-CoA:diacylglycerol acyltransferase (ADGAT) illustrates why relatively little triacylglycerol (TAG) may be incorporated into very low density lipoproteins (VLDL), and why EPA and DHA are preferentially found in certain phospholipids [18,19].

4.3 Membrane fluidity

When large amounts of very long-chain omega-3 fatty acids are ingested, there is high incorporation of EPA and DHA into membrane phospholipids, which may alter the physical characteristics of cell membranes [20]. Altered fluidity may lead to changes of membrane protein functions. The very large amount of DHA in phosphatidyl ethanolamine (PE) and phosphatidyl serine (PS) found in certain areas of the retinal rod outer segments, is probably crucial for the function of membrane phospholipids in light transduction, as these lipids are located close to the rhodopsin molecules [21]. It has been shown that the flexibility of membranes of blood cells from animals fed fish oil is markedly increased [22, 23], and this might be important for the microcirculation, particularly in cold environments. It seems as if phosphatidyl choline (PC) membranes containing DHA support faster flip-flop and permeability rates than other less unsaturated PCs [24]. Whole blood viscosity is reduced during fish oil feeding [25,26], and increased incorporation of very long-chain omega-3 fatty acids into plasma lipoproteins changes the physical properties of low density lipoprotein (LDL), promoting reduced melting point of core cholesteryl esters [27].

4.4 Lipid peroxidation

Lipid peroxidation products may act as biological signals in certain cells [12]. One of the major concerns with intake of omega-3 fatty acids has been the high degree of unsaturation and thereby the possibility of promoting peroxidation. Modified LDL might be endocytosed by macrophages and initiate development of atherosclerosis. Oxidatively modified LDL has been observed in atherosclerotic lesions [28], and LDL rich in oleic acid has been found to be more resistant to oxidative modification than LDL enriched with omega-6 fatty acids in rabbits [29].

There are several ways to quantify the degree of lipid peroxidation. Diene conjugation of PUFA, degradation of PUFA, appearance of lipid peroxides (LPO), appearance of thiobabituric acid reactive substances (TBARS), and antibodies against oxidized LDL have all been used to evaluate lipid peroxidation *in vivo* [30]. There is also some evidence that expired ethane is a measure of peroxidized omega-3 fatty acids, although this is not yet well established [31]. Many experiments have been performed to examine if di- etary intake of omega-3 fatty acids is associated with increased lipid peroxidation in humans [30]. The results of these studies are somewhat controversial. In many of the studies demonstrating enhanced LDL oxidation after omega-3 fatty acid supplementation, conclusions are based on measurement of the amount of thiobarbituric acid reactive substances (TBARS) formed during oxidation [32-35]. Because TBARS are oxidation products of fatty acids containing three or more double bonds, variations in TBARS production reflect the lipid composition rather than the susceptibility to lipid peroxidation [36].

Some studies have focused on the susceptibility of LDL isolated from subjects on different diets, to be oxidized *in vitro* in the presence of copper or azo-derivatives [30]. In these cases the diene conjugation, fatty acid pattern, LPO-formation, electrophoretic mobility of LDL and uptake in macrophages have been measured before and after incubation with the oxidizing agents [30,32-35]. Although the hypothesis of oxidative modification of LDL is supported by many observations, it is still unclear which of the above mentioned parameters that reflects the development of atherosclerosis. It is possible that omega-3 fatty acids may influence another player in the modification of LDL *in vivo*, the mono- nuclear cells. These cells may release enzymes or H2O2 that may modify LDL and thereby promote LDL uptake by macrophages in the vessel wall. This was examined by supplementing male smokers with combined hyperlipidemia with very long-chain omega-3 fatty acids and with moderate amounts of antioxidants in a randomized, double-blind placebo controlled trial [37]. With advanced methods to measure oxidation of circulating LDL from high-risk subjects, there was no significant

increase in lipid peroxidation after intake of 5 g/day of very long-chain omega-3 fatty acids for 6 weeks.

Some data suggest that intracellular hepatic lipid peroxidation might explain some of the hypolipidemic effects of dietary PUFA via increased post-ER pre-secretory proteolysis of apoB100 degra- dation [38].

Unesterified DHA is chemically highly susceptible to peroxidation, potentially forming several bioactive lipid peroxides. One class of compounds is cyclopentenone neuroprostanes, which is very reactive and structurally similar to anti-inflammatory cyclopen- tenone prostaglandins. Some of these neuroprostanes are potent inhibitors of nuclear factor kB (NF-kB) signaling and may contribute to the anti-inflammatory actions of DHA ([39].

4.5 Inflammatory Processes.

The susceptibility of fatty acids to oxidation is often assumed to be directly related to the degree of unsaturation. However, some *in vitro* and *in vivo* studies suggest that the relation between chemical structure and peroxidation susceptibility is less straightforward than deduced from a chemical point of view. Based on *in vivo* data demonstrating unaltered or reduced formation of lipid peroxidation products after omega-3 fatty acid intake [37,40], and more recent data on reactive oxygen species (ROS) production and direct superoxide scavenging by the omega-3 fatty acids, it is possible that these fatty acids might act as indi- rect anti- rather than pro-oxidants [41]. Although some of the published data are conflicting [42], several of the well-performed and widely accepted studies indicate few or no harmful effects of omega-3 fatty acids. In some cases it seems as if EPA and DHA promote less peroxidation as compared to shorter PUFA with fewer double bonds [43]. Based on epidemiological studies it should be noticed that the dietary amount of saturated fatty acids, trans-fatty acids and cholesterol are the lipids that are positively correlated with the development of coronary heart diseases, whereas the amount of PUFA is negatively correlated with the incidence of coronary heart diseases [8,11]. It is suggested that proper amounts of antioxidants are required with increased intake of PUFA to minimize the risk of lipid peroxidation [30].

5. ACYLATION OF PROTEINS

Acylation of proteins is important for anchoring certain proteins in membranes or folding of the proteins, and it seems to be crucial for the function of these proteins [44,45]. Although saturated fatty acids are most commonly linked to proteins, omega-3 fatty acids may also acylate proteins [46]. It has been demonstrated that PUFAs (AA and EPA) may inhibit palmitoylation and alter membrane localization of a protein kinase (Fyn) [47], whereas C14:2 may be acylated to a protein kinase (Fyn), thereby altering its raft localization and promote reduced T cell signal transduction and inflammation [48].

6. GENE INTERACTIONS

Fatty acids or their derivatives (acyl-CoA or eicosanoids) may interact with nuclear receptor proteins that bind to certain regions of DNA and thereby alter transcription of these genes. The receptor protein, often interacting with another nuclear receptor, may, in combination with a fatty acid, function as a transcription factor. The first described example of this is the peroxisome proliferator activated receptor (PPAR) [49]. Fatty acids that are blocked from being β-oxidised, may be better ligands for PPAR than natural fatty acids [50]. PUFA may also influence expression of several glycolytic and lipogenic genes independent of PPAR [51,52]. Prostaglandin J2 (PGJ2), an eicosanoid derived from AA, may bind to PPAR, although this is controversial [53]. Fatty acids (EPA and DHA) as well as eicosandoids can bind directly to PPARα and PPARγ [54,55].

PUFAs have marked effects on gene expression by regulating the activity or abundance of three other families of transcription factors, including liver X receptors (LXRs) (α and β), hepatic nuclear factor-4 alfa (HNF-4α) and sterol regulatory element binding pro- teins (SREBPs) 1 and 2 [56]. These transcription factors play major roles in hepatic carbohydrate, fatty acid, triglyceride, cholesterol and bile acid metabolism. Non-esterified fatty acids or fatty acid metabolites bind to and regulate the activity of PPARs, LXRs and

HNF-4. In contrast, PUFAs regulate the nuclear abundance of SREB- Ps by controlling the proteolytic processing of SREBP precursors, or by regulating transcription of the SREBP-1c gene or turnover of mRNA (SREBP-1c). The omega-3 and omega-6 PUFAs are feed- forward activators of PPARs, whereas these same fatty acids are feed-back inhibitors of LXRs and SREBPs. Saturated fatty acyl coen- zyme A thioesters activate HNF-4α, whereas coenzyme A thioesters of PUFAs antagonize HNF-4α action. It has also been shown that PUFAs including DHA are ligands for another transcription factor, retinoid X receptor (RXR), which is important for expression of several genes regulated by different nutrients [57,58].

7. OMEGA-3 FATTY ACIDS AND DISEASES

7.1 Cardiovascular diseases:

Cardiovascular diseases can be due to several different genetic and environmental factors [59]. Cardiovascular diseases are mainly caused by atherosclerosis, and give rise to development of myocardial infarction, cerebral infarction, cognitive decline, and gangrene and loss of function in the extremities. In addition to being the most common cause of death in developed countries, cardiovascular diseases cause fear, sorrow, pain, serious handicaps and loss of productivity. Moreover, cardiovascular diseases are very expensive to treat.

It has been shown that dietary factors such as saturated and trans fatty acids, cholesterol, some coffee lipids and sodium, in addition to lack of omega-3 fatty acids may promote development of atherosclerosis [60-63]. Smoking, high blood pressure, high plasma concentration of homocysteine, diabetes mellitus, obesity and low physical activity are additional factors that promote development of atherosclerotic lesions. All these factors are influenced by genes, as well as environmental factors, resulting in the outlined conditions or so called risk factors.

7.2 Atherosclerosis:

Development of atherosclerosis is a very complex process in response to insults to the endothelium and smooth muscle cells in the vessel wall [61]. Atheros is a Greek word for porridge, pointing to the central necrotic area of the atherosclerotic plaque, whereas sclerosis indicates the hardening of the surrounding area typical of several chronic inflammations.

The first cell biological precursor of atherosclerosis may be the adhesion of monocytes to the endothelial cells in the middle-sized arteries, whereas the first macroscopic sign of atherosclerosis is the appearance of fatty streaks. These are small yellow/white elevations aligned in the longitudinal direction of the arteries just beneath the endothelial cell layer, containing lipid-rich macro- phages and T-lymphocytes. These fatty streaks can develop into intermediate lesions loaded with lipid-rich macrophages and some smooth muscle cells. These lesions may develop further into fibrous plaques that contain a fibrous cap, more lipids, more inflammatory cells and some necrotic tissue with a significant amount of cholesterol mainly derived from digested LDL-particles. Blood platelets are attracted to the dysfunctional endothelium covering the lesion. Activation of several types of hydrolytic enzymes may lead to weakening of the fibrous cap and plaque rup- ture, promoting release of dead material (debris) into the blood stream. This is followed by immediate coagulation and thereby reduction of blood flow to an extent where the tissue may die [64]. Thus, development of atherosclerosis is related to disturbance of the vessel wall functions including diffusion of lipoproteins; expression of adhesion molecules on the surface of endothelial cells and white blood cells; adhesion of white blood cells to the endothelium; and migration of these inflammatory cells between the endothelial cells into the intima of the arteries. LDL diffuses into the vessel wall and interacts with proteoglycans in the subendothelial space before it may be modified by oxidation and taken up via specialized scavenger receptors in macrophages, causing accumulation of cholesteryl esters and lipid loaded “foam” cells.

7.3 Arrhythmias:

In cells and animal studies it has been shown that incorpora- tion of marine omega-3 fatty acids reduces the risk of arrhyth- mias, probably due to inhibition of the fast voltage-dependent sodium-channel [65,66]. Arrhythmias causing sudden cardiac death often arise from ischemia induced

electrical instability in the heart muscle. Ischemia may promote depolarization of cardiac membranes by reducing the activity of sodium/potassium ATPase, which enhances interstitial potassium concentration, making the resting membrane potential more positive. This may make myo- cytes more likely to depolarize due to small stimuli and thereby initiate an arrhythmia [67].

7.4 Human studies:

In spite of indications based on animal studies we have to rely on data from humans based on epidemiological, clinical and laboratory studies. These human studies suggest that very long-chain omega-3 fatty acids may be important in preventing development of atherosclerosis as well as thromboembolic events [68-75]. There are, however, some reports of no beneficial effects of omega-3 fatty acids [76-78], and a number of studies have not shown an inverse correlation between fish consumption and coronary heart disease [79,80].

7.5 Sudden death:

The cardioprotective effects of fish oil have been attributed to antiarrhythmic effects of EPA plus DHA [81]. Some clinical trials have examined whether omega-3 fatty-acid supplementation af- fects arrhythmias in patients with implantable cardioverter defi- brillators (ICD).

DHA vs. placebo and found significant reduction in time to first ICD discharge, with most benefit observed among patients with preexisting CHD. In contrast, Raitt et al. [83] observed no benefit of EPA + DHA (1.3 g/day), although they excluded patients with recent myocardial infarction. The most recent clinical trial included 546 patients with ICDs, randomized to either 0.8 g/day of EPA + DHA or control, to assess appropriate ICD discharges for ventricular tachycardia/ventricular fibrillation [84]. Whereas no difference in the primary endpoint was observed, there was a trend (P = 0.13) towards longer event-free survival in the EPA + DHA group among the prespecified subgroup with prior Myocardial infarction (n =342). Although the authors of this study concluded that their results did not indicate a strong protective effect of intake of marine omega-3 PUFAs against ventricular arrhythmia in patients with ICDs, Harris et al concluded in their review that the data sup- port the use of omega-3 fatty acids in post-Myocardial infarction patients with or without ICD placement. However, in non-ischemic patients with ICDs, there is little support for the use of fish oils in arrhythmia suppression.

7.6 Cancer:

In spite of the fact that animal fat is associated with many of the carcinogenic effects of dietary fat [84], there is some scientific evidence that omega-3 fatty acids may protect against develop- ment of certain types of cancers [85,86]. In a study including 24European countries, fish and fish oil consumption were shown to protect against the later promotional stages of colorectal carcinogenesis [86]. Augustsson et al [87] found that men who ate fish more than 3 times a week, had lower risk of prostate cancer (the strongest association was found for metastatic cancer) compared with those who ate fish less than twice per month. Additional in- take of long-chain omega-3 fatty acids (0.5 g/d from food) was associated with 24% reduced risk of metastatic cancer.

Although the extensive report on “Food, nutrition, physical activity and the prevention of cancer: a global perspective“ by World Cancer Research Fund and the American Institute for Cancer Resaerch,

2007 [88], concluded that there is limited evidence suggesting that eating fish protects against colorectal cancer, there are several recent studies reporting beneficial effects on risk of developing colorectal cancer [89,90]. The findings are, however, mixed [91].

In patients with an abnormal rectal cell proliferation pattern, low- dose fish oil supplementation had both short-term and long-term normalizing effects [92]. Similar results were obtained in a study on patients with colon or rectum adenocarcinoma [93]. In a prospective cohort study including more than 34 000 American women,[94] suggested that higher intake of omega-3 fatty acids may reduce the progression of small adenomas to large adenomas.

7.7 Rheumatoid arthritis / joints:

Several studies have shown that dietary supplementation with very long-chain omega-3

fatty acids (>3 g/day) reduces the clini- cal symptoms of rheumatoid arthritis as evaluated by morning stiffness and number of swollen joints, in meta-analyses [95,96]. It also appears that the amount of nonsteroid anti-inflammatory drugs (NSAIDs) commonly used by patients, may be reduced or even discontinued if very long-chain omega-3 fatty acids are sup- plied [97,98]. Although the clinical impact of very long-chain omega-3 fatty acids is less than that provided by drugs normally given for rheumatoid arthritis, the effect is significant and virtually without side effects [99,100].

7.8 Psoriasis:

Even though there may be some positive effects of very long-chain omega-3 fatty acids for patients with psoriasis [101,102], there are some very well controlled and large clinical studies demonstrating no significant effect of supplementing these fatty acids as compared to omega-6 fatty acids [103,104]. Still, it is possible that some subgroups of psoriatic patients would benefit from using omega-3 fatty acids in combination with other treatments [105] or as intravenous injection [106].

7.9 Atopic dermatitis:

The intake of vitamin D and very long-chain omega-3 fatty acids was shown to be low among a group of 138 Norwegian patients with atopic dermatitis, especially among female patients [107]. In a small controlled randomized clinical trial including patients with atopic dermatitis, dietary supplementation with very long chain omega-3 fatty acids lead to positive effects on subjective symptoms, compared to supplementation with olive oil [108]. However, in two large clinical intervention trials including 268 patients with moderate to severe atopic dermatitis, no difference was found between supplementation with fish oil and oils with high amounts of omega-6 fatty acids [109,110]. It should be noted that both the intervention group and the control group improved objectively as well as subjectively during the 4 month treatment period in the largest study [111]. Thus, it is possible that both omega-3 and omega-6 fatty acids might have a beneficial effect on this condition, as pointed out in more recent studies [112]. Iv administration of omega-3 fatty acids acutely (up to 10 days) improved the clinical status of atopic dermatitis, but the long-term effect is unknown [113].

7.10 Inflammatory bowel diseases:

There have been some large clinical trials on patients with Crohn's disease [114,115,116]. In these studies patients in remission received omega-3 fatty acids or control treatment for up to approximately one year. In one of the studies [114] omega-3 fatty acids signifi- cantly reduced the rate of relapse, whereas there was no significant effect in the other studies [114,115].

In a meta-analysis of randomized and double-blinded studies in patients with ulcerous colitis, there was no significant effect of supplementation with omega-3 fatty acids on clinical outcomes [117]. Although it is still unclear which groups of patients with inflammatory bowel diseases might benefit from supplementation with omega-3 fatty acids, it should be considered a realistic therapeutic option.

7.11 Asthma and allergy:

Data from a prospective epidemiological study suggested that regular dietary intake of fish was associated with better pulmonary function [118]. However, in a clinical trial with asthmatic patients, no improvement with omega-3 fatty acid supplementation was observed [119]. In a randomized controlled study among asthmatic children, the results suggest that dietary supplementation with long-chain omega-3 fatty acids was beneficial in a strictly control- led environment in terms of inhalant allergens and diet [120].

Higher omega-3 fatty acid levels in the colostrum did not protect against development of atopy in a prospective study among high- risk breastfed infants [121], whereas a potential reduction in infant allergy after maternal intake of long-chain omega-3 fatty acids among atopic mothers was shown in a randomized, controlled trial [122]. It has also been reported that dietary fish oil supplementation has a protective effect in suppressing exercise-induced bronchoconstriction among elite athletes [123]. Another study by Olsen et al. [124] suggest that there might be a beneficial effect of supplementing pregnant momen with 2.7 grams of

marine omega-3 fatty acids during the last 10 weeks of pregnancy. Assuming that intake of olive oil was inert, the results support that increasing n-3 PUFAs in late pregnancy may have a prophylactic potential in relation to offspring asthma.

Some experimental data on mice suggest that resolvins (derived from EPA) promote resolution of inflammatory airway responses in part by directly suppressing the production of IL-23 and IL-6 in the lung [125]. Also contributing to the pro-resolution effects of resolvin treatment were higher concentrations of interferon-gamma in the lungs of RvE1-treated mice.

7.12 Diabetes:

Some reports have indicated that supplementation with very long-chain omega-3 fatty acids causes the blood glucose level to increase among non-insulin-dependent diabetics (NIDDM). Although this observation is somewhat controversial [126], a number of reports suggest no or few negative effects of omega-3 fatty acid supplementation on glucose metabolism in hypertensives [127] or hypertriacyl-glycerolemics [128] or patients with coronary heart diseases [129]. Because of the many positive ef- fects of very long-chain omega-3 fatty acids, like reduced plasma concentrations of TAG and of free fatty acids, reduced blood pres- sure, reduced platelet agreeability and even increased insulin sensitivity in animals [130], it has been advised that patients with noninsulin dependent diabetes mellitus (NIDDM) may benefit from supplementation with small to moderate amounts of ma- rine oils [131]. In a meta-analysis it was concluded that intake of omega-3 fatty acids had no significant effect on glycemic control or fasting insulin [132].

An interesting observation is that Alaskan natives with high in- take of very long-chain omega-3 fatty acids exhibit reduced risk of developing NIDDM [133]. Hu et al [134] examined prospectively the association between intake of fish and omega-3 fatty acids and risk of CHD and total mortality among 5103 female nurses with diagnosed type 2 diabetes, but free of cardiovascular disease or cancer at baseline. They report that a higher consumption of fish and long-chain omega-3 fatty acids was associated with a lower CHD incidence and total mortality among diabetic women.

7.13 Obesity:

Obesity is a global and rapidly increasing disease [135] that is closely associated with development of inflammatory markers like enhanced plasma concentration of TNFα, IL-6, CRP, sialic acid, orosomucoid and alpha1-antichymotrypsin [136]. These markers are adipokines (protein hormones secreted from the adipose tissue like TNFα, IL-6 and CRP) or acute phase proteins (like CRP, sialic acid, orosomucoid and a1-antichymotrypsin). Although there is data suggesting a relation between inflammation and obesity [137], the inflammatory markers are often hard to detect [138]. Inflammation may represent a link between obesity and complications of obesity (eg cardiovascular diseases and diabetes type II [139]. Supplementation of omega-3 fatty acids may have a significant beneficial effect on insulin sensitivity among individuals with high markers of inflammation, whereas there appears to be little effect in subjects with small signs of inflammatory response [140]. These observations might explain the large difference in effects reported using supplements with marine fatty acids in patients with type II diabetes.

8. OMEGA-3 FATTY ACIDS AND CENTRAL NERVOUS SYSTEM

Several reports have suggested that supplementation with ma- rine omega-3 fatty acids are important for treatment of schizophrenia, depressions or borderline personality disorder [141-145]. Yet in other studies, no differences were found between groups in positive or negative symptoms, mood, cognition, or global impression ratings [146,147]. In a double-blind, placebo-controlled trial including 302 subjects over the age of 65, supplementation of 1800 or 400 mg EPA plus DHA daily for 26 weeks caused no effect on mental well-being [148]. Although there are some indications of improved central nervous function with enhanced intake of long-chain omega-3 fatty acids, the studies are small, short-term and often with low dosage. There is, therefore, a need for larger placebo-controlled randomized trials to evaluate if

omega-3 fatty acid supplementation will benefit patients with serious psychiatric disorders.

8.1 Depressions

Frangou et al (149) examined the efficacy of EPA in treating depres- sion in bipolar disorder in a 12-week, double-blind study by giving 1 or 2 gram/day of EPA ethylester as compared to a control group. Significant improvement was noted with ethyl-EPA supplementa- tion irrespective of dose, as compared to placebo in the Hamilton Rating Scale for Depression (P=0.04) and the Clinical Global Impression Scale (P=0.004) scores. However, a meta-analysis showed that four other small studies demonstrated no significant beneficial effect of omega-3 fatty acid supplementation of patients with bipolar disease [150].

Severus et al. [151] present data connecting cardiovascular disease, depression, omega-3 fatty acids and homocysteine, suggesting that omega-3 fatty acids, as well as homocysteine, might be closely related to depression.

8.2 Schizophrenia

Data indicate that the level of omega-3 fatty acids is low in red blood cells as well as in some cortical areas of the brain in schizophrenic patients [152,153], although the data are based on very small numbers of cases and are somewhat controversial [154]. The intervention studies on high risk subjects or chronic schizophrenics are also small and the results are not solid enough to recommend anything other than new, large and better designed studies in the future.

8.3 Alzheimer's and Parkinson disease

The risk of developing Alzheimer's disease (AD) has been inversely related to the dietary intake of fish in several epidemiological studies [155,156]. The omega-3 fatty acids in fish might explain part of this beneficial effect. It is clearly possible to influence the con- tent of DHA in the brain by dietary intake. In two prospective studies it was observed that lower plasma DHA levels increased the risk of developing AD later in life [157].

There are too few data on Parkinson disease in relation to dietary intake of omega-3 fatty acids to conclude on the potential effects of supplementation.

8.4 Attention deficit hyperactivity disorder (ADHD)

Dietary intake of omega-3 fatty acids has been linked to ADHD and related disorders in some studies (158). The Oxford-Durham randomized, controlled trial was conducted with 117 children with developmental coordination disorder (DCD) aged between 5–12 years. The children were supplemented with 730 mg of EPA plus DHA and 60 mg of gamma-linolenic acid (18:3,n-6), or a control. Intervention for 3 months in parallel groups, was followed by a 1-way crossover from placebo to active treatment for an addition- al 3 months. No effect of treatment was apparent on motor skills but significant improvements for active intervention versus placebo were observed in reading, spelling, and behaviour during 3 months in parallel groups. After the crossover, similar changes were seen in the placebo-active group, whereas children continuing with active treatment maintained or improved their progress.

Another study included a randomized, 3-months, omega-3 and -6 placebo-controlled, one-way crossover trial with 75 children and adolescents (8–18 years), followed by 3 months with omega-3 and -6 for all . The majority of subjects did not respond to omega-3 and -6 fatty acid supplementation. However, a subgroup representing 26% of subjects responded with more than a 25% reduction of ADHD symptoms and a drop of Clinical Global Impression scores to the near-normal range. After 6 months, 47% of all treated subjects showed such improvement. These responders tended to have ADHD inattentive subtype and co-morbid neurodevelopmental disorders .

In spite of these findings the data are too scarce to recommend specific therapy for ADHD-like conditions before more studies have demonstrated beneficial effects.

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