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Review article

Alteration of polyunsaturated fatty acid status and metabolism in health and disease

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Abstract – Essential polyunsaturated fatty acids (PUFA) cannot be synthesised in the body and must be ingested by food. A balanced intake of both n-6 and n-3 PUFA is essential for good health. PUFA are the basic constituents of phospholipid membranes and determine cellular membrane fluidity and modulate enzyme activities, carriers and membrane receptors. They are also precursors of active metabolites known collectively as eicosanoids (prostaglandins, prostacyclins, thromboxanes and leukotrienes) which regulate our cellular functions. Studies indicate that n-3 PUFA have anti-inflammatory, antithrombotic, antiarrhythmic actions and immuno-modulating properties. Erythrocyte fatty acid status is a reflection of dietary fat intake. It also explores PUFA metabolism and gives information about the integration of these fatty acids into cellular membranes. Thus, erythrocyte fatty acid analysis can detect PUFA insufficiencies and imbalances from the diet, but also metabolic abnormalities and lipid peroxidation. It can be helpful in the prevention and the control of chronic diseases in which PUFA alterations have been observed as coronary heart diseases, hypertension, cancer, diabetes, inflammatory and auto-immune disorders, atopic eczema, Alzheimer dementia, major depression, schizophrenia, multiple sclerosis, etc.

essential fatty acids / erythrocytes / metabolism / chronic diseases

1. INTRODUCTION

Fatty acids carry out many functions that are necessary for normal physiological health. Saturated fatty acids are non essential fatty acids and are harmful if ingested excessively in food. They favour excess weight, insulin resistance [1], increased LDL cholesterol and are atherogenic [2]. On the contrary, non essential monounsaturated fatty acids, and namely its main component oleic acid, have a beneficial effect upon cholesterol metabolism and a protective role against cardiovascular diseases [3].

Polyunsaturated fatty acids (PUFA) are designated as "essential" for good health as their metabolic precursors cannot be synthesised in the body and must be ingested by food intake [4]. PUFA have important effects on the structure and physical properties of localised membrane domains. They modulate enzyme activities, carriers and membrane receptors (low density lipoprotein LDL receptors, insulin, antibodies neurotransmitters, drugs receptors, etc.). PUFA are involved in eicosanoid (prostaglandins, prostacyclins, thromboxanes, leukotrienes) production, signal transduction, and the activation of nuclear transcription factors [5]. Parent essential fatty acids are linoleic acid (18:2 n-6) and α-linolenic acid (18:3 n-3) [6]. After their absorption, they are metabolised by chain elongation and desaturation to long-chain polyunsaturated

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fatty acids containing 20 or more carbon atoms of the n-6 family (arachidonic acid 20:4 n-6) and n-3 family (eicosapentaenoic acid [EPA] 20:5 n-3 and docosahexaenoic acid [DHA] 22: 6 n-3).

Δ6 desaturase, the first step of the desaturation–elongation pathway, plays a crucial role in PUFA biosynthesis. It requires activators: zinc, magnesium, vitamins B3, B6, B8, C and insulin. This enzyme is inhibited by chronic diseases and the ageing process. If Δ6 desaturation is impaired for any reason, the dietary supply of further essential precursors may be inadequate for normal function [7]. Like arachidonic acid, EPA is a substrate for synthesis of the eicosanoid mediators produced by the cyclooxygenase and lipooxygenase enzymes [8] and thus competes with arachidonic acid for the same metabolic pathways. Eicosanoids of the "2" series produced from arachidonic acid have pro-inflammatory, pro-aggregating, vasoconstriction action and immunosuppressive properties. Those of the "3" series produced from EPA have anti-inflammatory, anti-aggregating, vasodilatory and antiarythmic actions and immuno-modulating properties. DHA is especially important in the development of the brain, the retina and the spermatozoids [9]. Other actions of DHA include the formation of free radicals in response to oxidative stress [10], transcriptional activation of genes [11] and the prevention of apoptosis [12].

Impaired PUFA status is observed in numerous physiological state and chronic diseases. Thus, the early diagnosis of such impairment is of crucial importance, since it is recognized that the dietary PUFA intake could help in the prevention and the control of chronic diseases. PUFA status in Human can be assessed on several blood lipid classes. Whole plasma lipids present no interest because their fatty acid profile depends mainly on the proportion of the different lipid classes, which may vary considerably. On the opposite, erythrocyte phospholipid fatty acid status presents several advantages: (1) it is a reflexion spread over time of habitual dietary fat intake in relation to the biological half life of erythrocytes [13]; (2) the level of EPA can be used as a specific marker for the intake of fish and fish oil [14]; (3) phospholipids are a model of fatty acid incorporation into a cellular membrane; (4) it explores hepatic and extrahepatic fatty acid metabolism; (5) erythrocyte phospholipids are in equilibrium with structural phospholipids of tissues; (6) it has been correlated reasonably well with the food- frequency questionnaire (ffp) for the dietary intakes of polyunsaturated fatty acids [15]. However the ffp is long and tedious and can lack accuracy in comparison with the precision of erythrocyte fatty acid measurements. This article reviews the current evidence regarding changes in fatty acid status (Tab. I) and therefore in PUFA metabolism in human in different states (smoking, hormonal contraception, pregnancy) and chronic diseases, and explores the beneficial potential effects of dietary supplementation with PUFA.

2. SMOKING, HORMONAL CONTRACEPTION, PREGNANCY AND PREMENSTRUAL SYNDROME

Free radicals generated in cigarette smoke are known to deplete antioxidants and may result in increased lipid peroxidation which leads to decreased concentrations of long chain PUFA. This may be due to an inhibitory effect of tobacco, or its metabolites on erythrocyte fatty acid metabolism as their PUFA content was decreased. The negative effect of cigarette smoking on PUFA stores may be one further mechanism by which cigarette smoking promotes vascular disease [16].

A potential adverse effect of hormonal contraception on erythrocyte fatty acid status has been observed by increasing some saturated fatty acids such as C16:0 and decreasing other unsaturated fatty acids such as EPA [17]. PUFA play an important role

Table I. Changes in erythrocyte fatty acid metabolism from smoking patients, from women under hormonal contraception or in pregnant and in different chronic diseases.

	Saturate fatty acids	Monounsaturated fatty acids	Long-chain polyunsaturated fatty acids	References
Smoking			↘	[16]
Hormonal conception			↘	[17]
Pregnancy	↗		↘	[21]
Coronary heart disease	↗		↘	[25]
Diabetes			↘	[7]
Cancer			↘	[44, 45]
Atopic eczema-psoriasisS			↘	[49]
Crohn's disease			↘	[57]
Cystic fibrosis		↗	↘	[60]
Multiple sclerosis			↘	[62, 79]
Alzheimer dementia			↘	[66]
Major depression			↘	[67]
Schizophrenia			↘	[71, 74]

in the brain and vascular development and in the normal course of pregnancy, as well as in a number of conditions as fetal growth retardation [18] and preeclampsia [19, 20]. During pregnancy, there is a faster turnover of PUFA from fast storage that may modify the profile of erythrocyte cell membrane fatty acids [15]. A significant decrease in the proportion of n-3 PUFA from the first to the third trimester has been noted [21]. Thus, it is suggested that n-3 PUFA intake during pregnancy should be increased in the last trimester.

Menstrual pain or dysmenorrhea is the most common gynecological complaint among female adolescents and young women. The majority of dysmenorrhea has a physiologic cause, with occasional psychological components. The high intake of n-6 fatty acids in the western diet results in a predominance of these fatty acids in the cell membrane phospholipids. After the onset of progesterone withdrawal before menstruation, these n-6 fatty acids, particularly arachidonic acid, are released, and a cascade of prostaglandins and leukotrienes is initiated in the uterus [22]. The inflammatory response, which is mediated by these eicosanoids produces both cramps and systemic symptoms such as nausea, vomiting, bloating and headaches. The prostaglandins E_2 and $F_{2\alpha}$, cycloxygenase metabolites of arachidonic acid, cause especially potent vasoconstriction and myometrial contractions, which lead to ischemia, pain and systemic symptoms of dysmenorrhoea. Several double blind, placebo controlled trial studies have demonstrated that dietary supplementation with n-3 fatty acids has a beneficial effect on symptoms of dysmenorrhea [23, 24]. EPA and DHA compete with arachidonic acid for the production of prostaglandins and leukotrienes through the incorporation into cell membrane phospholipids and through competition at the prostaglandin synthesis level. PUFA n-3 can also inhibit arachidonic acid formation at the level of the $\Delta 6$ desaturase enzyme [23]. In the uterus, this competitive interaction between n-3 and n-6 fatty acids may result in the production of less potent prostaglandins and leukotrienes and may lead to a reduction in the systemic symptoms of dysmenorrhea [22].

3. CORONARY HEART DISEASE

Altered fatty acid metabolism has been reported in patients with angiographically documented coronary disease [25]). Carotid intima-media thickness has been associated significantly and positively with saturated fatty acids and inversely with n-3 PUFA composition in both plasma phospholipids and cholesterol esters [2]. The n-3 fatty acids of fish and fish oil have great potential for the prevention and treatment of patients with coronary artery disease. One of the most important effects of n-3 EPA and DHA is their ability to inhibit ventricular fibrillation and consequent cardiac arrest in primary and secondary prevention [26, 27]. EPA has antiarrhythmic effects and several antithrombotic actions, particularly inhibiting the synthesis of thromboxane A_2, the prostaglandin that causes platelet aggregation and vasoconstriction. Fish oil retards the growth of the atherosclerotic plaque by reducing pro-inflammatory interleukine 1 (IL1) and tumour necrosis factor (TNF) and by inhibiting both cellular growth factors and the migration of monocytes. The n-3 fatty acids promote the synthesis of the beneficial nitric acid oxide in the endothelium. Experiments in humans indicate a hypolipemic effect of fish oil, especially the lowering of plasma triglyceride [28].

4. HYPERTENSION

Different mechanisms appear to be involved in hypertension. Changes were reported in eicosanoid metabolism, viscosity, loss of sodium, increase in potassium in cells and a decrease in intracellular calcium, among others [29]. In clinical studies, α-linolenic acid contributed to the lowering of blood pressure [30, 31]. In a population- based intervention trial it has been reported that a relationship may exist between n-3 fatty acid concentration in plasma phospholipids and blood pressure. There was a lower blood pressure at the baseline in subjects who habitually consume large quantities of fish, suggesting that supplementation with fish oils would be important from the primary prevention standpoint [32].

5. DIABETES

Type 2 diabetes is a multigenic, multifactorial disorder. There is an interaction with genetic predisposition, diet and exercise in the development of this disease. Type 2 diabetes is characterised by hyperglycemia, insulin resistance and vascular complications. In animal studies, increasing the content of polyunsaturated fatty acids in the cell membrane enhances the insulin receptor number and binding and insulin action while saturated fat decreases binding and transport [33]. Limited clinical studies are suggestive of a similar effect [22].

In diabetic patients the concentrations of linoleic acid metabolites (γ-linolenic acid GLA 18:3n-6 and arachidonic acid) are consistently below normal in erythrocytes [7]. The reason is that in diabetes the Δ6–Δ5 desaturase enzyme activities are greatly impaired [7]. Decreased content of long chain polyunsaturated fatty acids, in particular arachidonic acid, and the total percentage of C_{20}–C_{22} polyunsaturates is associated with decreased insulin sensitivity [34].

In a recent clinical study on erythrocyte membranes, n-6 polyunsaturated fatty acids were positively correlated to insulin sensitivity while membrane saturated fatty acids appear to have the opposite effect [35]. Another study suggests that hyperinsulinemia and insulin resistance are inversely associated to the amount of 20 and 22 C PUFA in muscle cell membrane phospholipids in patients with coronary heart disease and in normal volunteers [36].

6. CANCER

Epidemiological studies have demonstrated that dietary fat consumption modulates the risk of several types of cancer,

especially breast, prostate and colorectal cancer [37, 38]. The relationship between the intake of specific fatty acids and the risk of cancer in humans has been investigated in several studies [39, 40]. Animal studies suggest that n-3 PUFA can inhibit the development of cancer, and that n-6 PUFA promote the development and growth of cancer [41, 42]. Some authors have observed that essential fatty acids and their metabolites can reverse and/or inhibit tumour cell drug resistance at least in vitro [43]. In a clinical study using a case-control, the level of α-linolenic acid was inversely related to the risk of developing metastases in breast cancer patients [44]. In a Japanese population study, an inverse association between prostate cancer mortality rate and serum n-3 PUFA levels appears to exist, but the results for other cancer mortality rates are not clear [45].

7. ATOPIC ECZEMA AND PSORIASIS

Atopic eczema is an inherited form of dermatitis that almost always develops initially during the first year of life. It remits and relapses throughout life, often showing considerable improvement around the time of puberty. Patients with atopic eczema have an abnormal immune function, with high concentrations of immunoglobulin E (IgE) and an elevated ratio of T-helper to T-suppressor lymphocytes [46].

Dermatitis is consistently the first sign of PUFA deficiency in both animals and humans. Adult patients with atopic eczema were compared with normal individuals with regards to the fatty acid composition of plasma phospholipids [47]. Linoleic acid (LA) concentration was slightly above normal while its metabolites GLA, dihomo-γ-linolenic acid (DGLA 20:3n-6) and arachidonic acid were below normal. Reduced LA metabolites has also been found in children with atopic eczema, in cord blood of babies at risk for atopic eczema, because of genetic history [48], in triglycerides of adipose tissue and in the breast milk of people with atopic eczema and at last in the red blood cells of patients with eczema [49]. This suggests that either Δ6 desaturase activity is somewhat reduced in atopic eczema, or that the consumption of the metabolites is excessive and could not be compensated by the rate- limiting enzyme. By-passing the Δ6 desaturase by giving GLA in the form of evening primrose oil led to a partial normalisation of fatty acid phospholipid composition and an increase in the formation of prostaglandin E1, thus producing clinical improvement [46]. In psoriasis, arachidonic acid metabolism is altered. Proinflammatory leukotrienes (leukotriene B4 LTB4) are markedly produced in the psoriatic lesions. The addition of fish oil to the standard treatment produces further improvement and a decrease in LTB4 [49]. This approach provides an alternative or adjunct protocol for the management of psoriasis and inflammatory skin disorders with negligible side effects [50].

8. RHEUMATOID ARTHRITIS (RA)

Investigations have examined the effects of dietary fatty acid supplementation in a variety of autoimmune diseases. The effects of both n-6 and n-3 fatty acids on rheumatoid arthritis has been reported [51, 52].

In a well designed study, investigators treated patients with RA with 1.4 g of GLA daily over a period of 24 weeks. They observed a clinically important reduction in both the tender and swollen joint counts of 36 and 38% of the patients respectively, while the placebo group showed no improvement in these parameters [53]. It has previously been demonstrated that GLA can inhibit interleukin-2 (IL-2) production and may reduce the activation of T lymphocytes [54].

The effects of a dietary fish oil supplement on active rheumatoid arthritis has also been shown in a double-blind study. Clinical improvements in tender joint scores and morning stiffness have been reported with

the fish oil [55]. In addition, fish oil supplements are associated with a decreased production of IL-1 and LTB4 which should aid in the amelioration of inflammation.

9. ULCERATIVE COLITIS

As indicated earlier, LTB4 a metabolite of arachidonic acid is produced by activated neutrophils and n-3 fatty acids decrease its production. LTB4 is an important mediator of inflammation in ulcerative colitis. A study of the effects of fish-oil supplementation was conducted on ulcerative colitis. Preliminary analysis showed a statistically significant improvement in sigmoidoscopy score and global clinical assessment after 4 months of a fish oil supplemented diet compared with a placebo diet in active ulcerative colitis [56].

In another double-blind, placebo-controlled study, fish oil seemed effective in reducing the rate of relapse in patients with Crohn's disease [57].

10. CHRONIC INTESTINAL FAILURE

Patients with chronic intestinal disorders or severe malabsorption often develop essential fatty acid deficiency. The deficiency can be corrected by intravenous lipids, but essential fatty acid abnormalitie persist. Stimulation of n-6 PUFA biosynthesis which could lead to an inhibition of n-3 PUFA elongation has been observed [58]. This could be related to the severe malabsorption.

11. CYSTIC FIBROSIS

Cystic fibrosis, a genetic disease, is characterised by thick mucus in the lungs and gastrointestinal tract, pancreatitis and pulmonary infection. Elevated concentrations of sodium and chloride are integral and diagnostic features. Abnormalities in the different phospholipid fractions of red cell membranes have been documented in cystic fibrosis patients [59]. Reduced levels of linoleic acid in association with increased oleic acid have been described [60]. Moreover, different investigators have demonstrated an increased turnover of arachidonic acid, the major substrate for the synthesis of the pro-inflammatory eicosanoids which could contribute to the pathology and clinical picture seen in cystic fibrosis [61].

12. MULTIPLE SCLEROSIS (MS)

Several studies suggest that modest abnormalities in linoleic acid and n-3 fatty acids profiles may exist in erythrocyte lipid fractions in multiple sclerosis patients [18, 62]. In a double-blind control trial of long chain n-3 PUFA in the treatment of MS, there was a trend in favour of the group treated with fish oil in all the parameters examined [63]. In another study there was a benefit effect of low saturated fat in early and late cases of MS. Patients taking a low-fat diet (≤ 20 g fat·day^{-1}) showed significantly less deterioration in neurological disability and lower death rates [64].

13. NOREULOGICAL DISEASES – ALZHEIMER DEMENTIA, DEPRESSION, ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD) AND SCHIZOPHRENIA

Docosahexaenoic acid (DHA) is the major acid of neurological and retinal membranes. It makes up more than 30% of the structural lipids of the neuron [65]. In a retrospective study including 1188 elderly American subjects, the authors suggest that low levels of circulating DHA may be a significant risk in the development of Alzheimer dementia. The inability to maintain a high level of DHA may be due to a reduced ability to synthesise DHA late in life as the result of a reduction in $\Delta 6$ desaturase activity [66].

Abnormalities in fatty acid composition may play a role in psychiatric disorders,

including depression. Alterations in phospholipids which are structural components of all cell membranes in the brain may induce changes in membrane fluidity and, consequently, in various neurotransmitter systems, which are thought to be related to the pathophysiology of major depression [48]. Depletion of n-3 fatty acid levels in red blood cell membranes of depressive patients has been reported [67]. A significant positive relationship has also been noted between the severity of the illness and the ratio of arachidonic acid to eicosapentaenoic acid in serum phospholipids and in erythrocyte membranes [68].

The condition of ADHD in children has many etiologies and is likely to be inherited in many cases. It is comprised of deficits in sustained attention, in impulse control, and in the regulation of the activity level to situational demands. These children are usually described as hyperactive from their early pre-school years. Biochemical research indicates an aberrant metabolism of dopaminergic transmitters in the central nervous system [69]. One hypothesis of the etiology of ADHD is concerned with the role of prostaglandins in the dopaminergic synapses. Prostaglandin E1 (PGE1) is considered to have a modulating function in the dopaminergic synapses, influencing the release of transmitters and the reaction to them. PGE_1 is synthesised from linoleic acid in several steps. The first step, from LA to gamma-linoleic acid (GLA) is catalysed by the enzyme $\Delta 6$ desaturase. According to this hypothesis, ADHD is caused or aggravated by a deficiency of PGE1 which is again caused by a lack of the enzyme. Abnormalities in PUFA metabolism in red blood cell membranes has been also reported in children with ADHA [70].

Several hypotheses have been advanced stating that genetic disturbances in phospholipid and prostaglandin metabolism may contribute to schizophrenic etiology and severity [71]. The observation that abnormalities in n-3 PUFA may play a critical role has been supported by reports of three types of essential fatty acid aberrations among schizophrenic patients [72, 73]. First, several authors have reported lower concentrations of erythrocyte essential fatty acids among schizophrenic patients as compared with control subjects [72, 74]. A second set of findings has correlated lower erythrocyte essential fatty acid concentrations with greater severity of negative symptoms [75, 76]. Third, findings of bimodal distributions of arachidonic acid, eicosapentaenoic acid and docosahexaenoic acid concentrations among schizophrenic patients have raised the possibility that distinct subgroups of schizophrenia could be identified based on abnormalities in fatty acid composition [77, 78].

14. CONCLUSIONS

Fatty acids carry out many functions that are necessary for normal physiological health. Chronic diseases are frequently associated with abnormalities in polyunsaturated fatty acid metabolism: coronary heart disease, hypertension, diabetes, cancer, inflammatory and autoimmune disorders, atopic eczema, depression, schizophrenia, Alzheimer dementia, multiple sclerosis, etc. (Tab. I). n-3 PUFA provide important health benefits. Erythrocyte fatty acid measurements can determine fatty acid deficiencies or imbalances from the diet, but also metabolic anomalies (lack of $\Delta 6$ desaturase) or to lipid peroxidation. Red blood cell fatty acid analysis can give information on cellular membrane fatty acid status and potential eicosanoid biosynthesis. Measuring erythrocyte fatty acids for the purpose of monitoring dietary fat intake or as a biomarker of disease risk is becoming increasingly common in clinical nutrition [79]. It can also be helpful for dietary advice in the prevention and the control of chronic diseases.

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