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Overview of Essential Fatty Acids: Types and Applications

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Abstract

Essential fatty acids (EFAs), including omega-3 and omega-6 polyunsaturated fatty acids (PUFAs), are crucial for maintaining cellular function and overall health. As the body cannot synthesize EFAs, they must be obtained through the diet. EFAs play key roles in various physiological processes, such as membrane fluidity, enzyme activity, gene expression, and the production of bioactive lipid mediators like eicosanoids. Omega-3 fatty acids (e.g., alpha-linolenic acid, ALA; eicosapentaenoic acid, EPA; and docosahexaenoic acid, DHA) are particularly noted for their anti-inflammatory, cardioprotective, and neuroprotective properties, while omega-6 fatty acids (e.g., linoleic acid, LA) are involved in inflammatory and immune responses. An imbalance between omega-3 and omega-6 intake, typically skewed towards excessive omega-6 consumption, is associated with an increased risk of chronic diseases such as cardiovascular disease, diabetes, arthritis, and certain types of cancer. Additionally, deficiencies or imbalances in EFAs can impair growth, cognitive function, and immune responses. Recent research has highlighted the importance of optimizing EFA intake for disease prevention and health promotion, particularly through dietary sources like fish, flaxseeds, walnuts, and vegetable oils. This abstract underscores the critical role of EFAs in both maintaining health and mitigating the risk of various chronic conditions.

Keywords: *Alpha-Linolenic Acid, Essential Fatty Acids, Free Fatty Acids, Omega 3.*

Introduction

Essential fatty acids (EFAs) are crucial components of all cell membranes, where they affect membrane fluidity and, consequently, influence the function of membrane-bound enzymes and receptors. EFAs are vital for human survival but cannot be synthesized by the body, meaning they must be obtained through diet. There are two main types of EFAs found in the body: the omega-6 series, derived from cis-linoleic acid (LA, 18:2), and the omega-3 series, derived from alpha-linolenic acid (ALA, 18:3). Additionally, there is a fatty acid derived from oleic acid (OA, 18:1 omega-9), but oleic acid is not considered an EFA. The omega-9, omega-6, and omega-3 fatty acids are all metabolized by the same set of enzymes into their respective long-chain derivatives. This discussion will focus on omega-6 LA and omega-3 ALA and their metabolites, as they are the primary EFAs. It's important to note that although some of the biological actions of EFAs depend on their conversion into eicosanoids and other products, in many cases, the EFAs themselves are directly active [1, 2].

Synthesis and Endogenous Components

Cell membranes are rich in lipids, primarily phospholipids composed of 3-carbon glycerol backbones. The sn-1 position (top carbon) typically holds a saturated fatty acid, such as palmitic acid (C16:0), stearic acid (C18:0), or oleic acid (monounsaturated). At the sn-2 position (middle carbon), arachidonic acid, DHA, or linoleic acid is usually present, though breast milk is an exception, placing palmitic acid here. The sn-3 position (lower carbon) often contains phosphate groups linked to various molecules like inflammatory cytokines,

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thromboxane (key in cardiovascular disease), and endocannabinoids, which influence inflammation, gut motility, temperature, appetite, obesity, and cardiovascular health. Variations in the 5-lipoxygenase gene significantly affect arachidonic acid metabolism, underscoring its role in cardiovascular disease [1].

Alpha-linolenic acid (ALA) predominantly undergoes β-oxidation but is also converted to EPA and DHA using the same enzymatic pathway as linoleic acid. Major phospholipid types include phosphatidic acid, phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine, and phosphatidylinositol. Linoleic acid makes up about 20% of fatty acids in human plasma phospholipids, while ALA accounts for 0.3%. In erythrocyte membranes, these values are 9% and 0.03%, respectively. Cardiolipin, a distinct phospholipid in the mitochondrial inner membrane, contains four fatty acid residues, 60-80% of which are linoleic acid, playing a crucial role in the electron transport chain [2].

Linoleic acid follows various metabolic pathways, including (a) β-oxidation to produce acetyl-CoA for energy via the Krebs cycle, (b) elongation to C26:2n-6, (c) conversion to arachidonic acid, adrenic acid (C22:4n-6), and docosapentaenoic acid n-6 (C22:5n-6), (d) formation of oxidative stress products like 4-hydroxynonenal and malonaldehyde, and (e) synthesis of 9- and 13-hydroxy- and oxo-derivatives via 12/15 lipoxygenase [3]. These derivatives undergo further processing; for example, arachidonic acid serves as a precursor for prostaglandins (pain mediators) and leukotrienes [4].

Figure 1 demonstrates the shared enzymatic pathway where linoleic and alpha-linolenic acids compete based on substrate availability. Only 0-4% of ingested alpha-linolenic acid (ALA) is converted to DHA, with men generally having a limited ability to synthesize DHA. When dietary linoleic acid intake is reduced from 10.5% to 3.8% of total energy in healthy men, while ALA intake remains constant at 1%, EPA synthesis increases. The incorporation of ALA into tissues and its conversion to DHA depend on the absolute dietary amounts of linoleic and alpha-linolenic acids rather than their ratio (e.g. 19:1 vs. 7:1). In cases where DHA production is insufficient or dietary DHA is lacking, docosapentaenoic acid (n-6), a less effective linoleic acid derivative, replaces DHA in membranes, resulting in reduced membrane fluidity and functionality. This highlights the significance of dietary EPA and DHA, particularly in the context of linoleic acid intake [3].

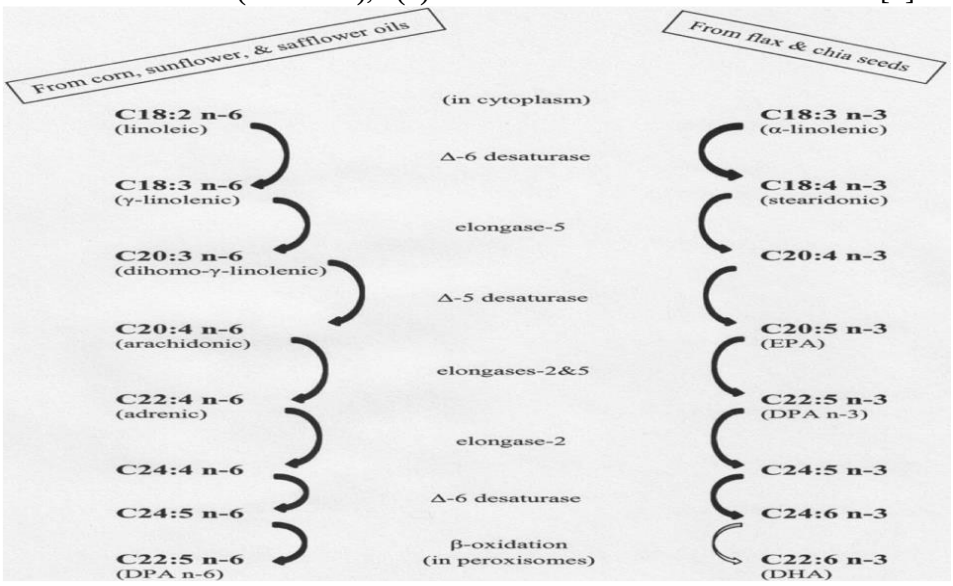

Figure1. The cascade of linoleic and a-linoleic acids, primary sources, and shared enzymes [3].

Arachidonic acid, EPA, and DHA are termed essential fatty acids due to their role in producing bioactive, highly unsaturated fatty acid derivatives. These derivatives, formed via cyclooxygenase, lipoxygenases, and cytochrome P-450 pathways, act as lipid mediators. While arachidonic acid metabolites are predominantly inflammatory, n-3-derived metabolites are generally anti-inflammatory, though their effects are complex. Some polyunsaturated fatty acids also act as ligands for nuclear receptors, including retinoid X-receptors and peroxisome proliferator-activated receptors (PPARs: alpha, beta, gamma, and delta), influencing gene transcription. EPA and DHA are strong regulators of hepatic gene expression, whereas ALA is a weaker regulator. DHA, for instance, activates retinoid X-receptors, while its oxidative product, 4-hydroxy-DHA, inhibits endothelial cell proliferation and angiogenesis via PPAR-gamma. Neuroprotectin D1, derived from DHA, promotes neuronal survival through PPAR-gamma and secretase mechanisms, particularly in Alzheimer's disease models [5].

PPAR-alpha regulates fatty acid oxidation and induces D-5 and D-6 desaturases through sterol-regulatory element binding protein-1c. Oxidative metabolites like 13-hydroxy-linoleic acid activate PPAR-gamma, while linoleic acid acts as an agonist for PPAR-alpha/delta, promoting osteoblast differentiation. For instance, a saturated-fat shake can upregulate specific genes, whereas a DHA-enriched shake downregulates them. A 26-week intake of 1.8 g/day EPA and DHA upregulates 1,040 genes involved in inflammation, atherogenesis, and related pathways, including NF-kappa B signalling, eicosanoid synthesis, and adipogenesis. In contrast, high-oleate sunflower oil alters the expression of only 298 genes. EPA and DHA also enhance PPAR-alpha (boosting fatty acid oxidation and lowering triglycerides) and PPAR-gamma (improving insulin sensitivity) [5].

DHA's six double bonds allow it to adopt over 100 configurations, making it a highly versatile molecule. It functions both as a structural component, accounting for about 14% of brain fatty acids, primarily in synaptic membranes, dendrites, and photoreceptors, and as a precursor for hydroxylated compounds like resolvins and protectins. Neuroprotectin D1, derived from DHA via 15-lipoxygenase-1, plays a crucial role after seizures or brain injuries by promoting synaptic and circuit integrity, reducing inflammation, and supporting cell survival. Additionally, DHA is essential for coordinating complex metabolic networks involving glucose, fatty acids, and amino acids, particularly to optimize dietary protein use during early development [6].

EPA serves as a precursor for E-resolvins, which are trihydroxylated molecules with strong anti-inflammatory properties, and for DHA. In the central nervous system, EPA is rapidly metabolized through β-oxidation within minutes. Translating the complexities of human fatty acid metabolism into clinical applications poses significant challenges [6, 7]:

1. **Species-Specific Differences**: Human fatty acid metabolism differs markedly from animals, compounded by human genetic polymorphisms.
2. **Dietary Intake Estimates**: Estimates of human intake are approximate, complicating the ability to demonstrate benefits in studies.
3. **Isocaloric Substitutions**: Changing macronutrient composition (carbohydrates, proteins, fats) in diets complicates study interpretations.
4. **Nutritional Influences**: Nutritional factors like vitamin D3 or taurine (common in fish-rich diets, e.g., Japan) may significantly influence disease outcomes.
5. **Biological vs. Statistical Norms**: Optimal tissue levels of fatty acids, such as EPA and DHA, are still being defined and are often modelled on populations like modern Japan, which may not universally apply.

6. **Measurement Challenges**: Fatty acid concentrations can be expressed as mole percentages or absolute values, with no consensus on the best approach for all contexts.

Furthermore, fundamental differences exist between evidence-based medicine and evidence-based nutrition. Randomized, double-blind, placebo-controlled trials are the gold standard in medicine for assessing drug efficacy, particularly for non-deficiency states, dose-related effects, and short-term outcomes. However, these methods are less suited for studying nutrients, which:

1. Primarily affects deficiency states (unethical to induce in humans).
2. Have polyvalent effects that may be obscured by biological noise.
3. Operate synergistically with other nutrients.
4. May show effects only over long periods.

Nutrient trials often compare different non-deficient intake levels rather than zero-intake groups, and the inherent complexity of food makes conclusive randomized controlled trials unlikely. In the case of fatty acids, a combination of evidence-based medicine and evidence-based nutrition approaches is necessary to address the intricate interplay of dietary factors and health outcomes [8].

Types of EFAs

Essential fatty acids (EFAs) are a type of polyunsaturated fatty acids (PUFAs), characterized by the presence of two or more double bonds in their carbon chain. These double bonds create a more fluid structure compared to saturated fatty acids, which lack double bonds. PUFAs are critical for various physiological functions, including cell membrane integrity, signalling, and inflammatory response [4].

There are at least four distinct families of PUFAs, each with unique structures and biological roles [4]:

1. **Omega-3 (ω-3) Family**: These PUFAs contain their first double bond at the third carbon from the methyl (omega) end of the molecule. The most well-known omega-3 EFAs are alpha-linolenic acid (ALA, 18:3), eicosapentaenoic acid (EPA, 20:5), and docosahexaenoic acid (DHA, 22:6). Omega-3 PUFAs are important for brain function, anti-inflammatory processes, and cardiovascular health.
2. **Omega-6 (ω-6) Family**: In these PUFAs, the first double bond is located at the sixth carbon from the omega end. The primary omega-6 EFA is linoleic acid (LA, 18:2), which can be further converted into other biologically active molecules like arachidonic acid (AA, 20:4). Omega-6 fatty acids play crucial roles in cell membrane structure, immune responses, and inflammation.
3. **Omega-9 (ω-9) Family**: Omega-9 fatty acids, such as oleic acid (OA, 18:1), have their first double bond at the ninth carbon from the omega end. Unlike omega-3 and omega-6 fatty acids, omega-9 fatty acids are not classified as essential because the body can synthesize them. However, they are still important for overall health, supporting heart health and reducing inflammation.
4. **Omega-7 (ω-7) Family**: Although less commonly discussed, omega-7 fatty acids, such as palmitoleic acid (16:1), are a smaller family of PUFAs that have a double bond at the seventh carbon. These fatty acids have been found to play roles in insulin sensitivity, lipid metabolism, and potentially in reducing inflammation.

These four families of PUFAs, each with distinct structures and metabolic pathways, contribute to a variety of biological functions. The balance between omega-3 and omega-6 PUFAs is particularly important, as both families influence inflammation and other cellular processes, but excessive omega-6 intake relative to omega-3s can promote pro-

inflammatory pathways. Thus, maintaining a healthy balance of PUFAs in the diet is crucial for overall health and disease prevention [4].

Actions of EFA

Actions on the Cardiovascular System

A high consumption of fish may help reduce mortality from coronary artery disease. In the DART study, patients who were randomly assigned to eat fatty fish twice a week experienced a 30% reduction in acute coronary syndrome events [9]. EPA and DHA, the key omega-3 fatty acids in fish, may help lower the incidence of arrhythmias, sudden cardiac death, atherosclerosis, and slightly reduce blood pressure. As a result, the American Heart Association (AHA) recommends consuming fatty fish at least twice a week or using fish oil as an adjunctive therapy to reduce cardiovascular disease risk [10]. Omega-3 fatty acids are also known to reduce serum triglyceride levels, but it remains unclear how much of the cardiovascular benefits are due to triglyceride-lowering effects and how much is attributed to other, triglyceride-independent mechanisms [4].

Omega-3 fatty acids may also help prevent atrial fibrillation, although research results have been mixed. Some studies suggest that EPA and DHA may influence the structural remodelling of the atrium. In a population-based study involving individuals aged 65 and older, those who consumed grilled or baked fish had a reduced risk of atrial fibrillation. Since this age group often has underlying cardiovascular conditions leading to atrial structural changes, fatty acid supplementation is thought to be beneficial in preventing atrial fibrillation caused by such structural remodelling [9].

While the cardiovascular benefits of fish consumption are well-established, there is limited evidence regarding the effectiveness of EPA/DHA supplementation (in fish oil capsules) in preventing heart attack, stroke, cardiovascular disease, sudden death, or overall mortality in the general population or among individuals with diagnosed cardiovascular conditions [11].

Actions on the Central Nervous System

For proper transmission of neural impulses, the neuronal membrane must allow an appropriate exchange of ions between its inner and outer surfaces. This exchange is regulated by the fluidity of the membrane. In peripheral membranes, factors such as dietary fatty acids, alcohol, aging, anaesthetic and psychoactive drugs, thyroid hormones, and iron overload can influence membrane fluidity. In the brain, membrane fluidity is particularly affected by dietary fatty acids, especially polyunsaturated fatty acids (PUFAs), as well as anaesthetic drugs, aging, and cholesterol levels. As a result, various factors can regulate neuronal transmission [12].

Additionally, free fatty acids (FAs) can modulate membrane proteins to help ion channels adjust to the passage of neuronal signals along the axon. This process is also influenced by lipid metabolites and phospholipids. The levels of essential fatty acids (EFAs) and the balance between omega-3 (n-3) and omega-6 (n-6) fatty acids are crucial for cognitive and biochemical functions. While omega-3 fatty acids increase dopamine receptor density, both n-3 and n-6 fatty acids contribute to lowering cholesterol levels through different mechanisms. These PUFAs can influence membrane fluidity, receptor formation and function, membrane signalling, and the activity of membrane-bound enzymes [3].

Emerging evidence suggests that fish consumption and the intake of EPA and DHA may offer protective effects against dementia and Alzheimer's disease, both of which involve progressive cognitive decline. Two primary mechanisms may explain these potential benefits of omega-3 fatty acids: first, their anti-inflammatory and cardiovascular protective effects, which reduce the risk of atherothrombotic complications and help prevent subsequent cognitive decline; second,

their role in improving cell membrane composition, which could promote nerve cell development and regeneration [12].

Epidemiological studies have associated fish consumption with a reduced risk of dementia. For individuals without the ApoE ε4 allele, lower intake of fish and fish oil and reduced plasma DHA levels have been linked to Alzheimer's disease, as well as impaired memory, cognition, and mood in adults over 65 years with depression. Postmortem analysis of three cortical brain regions revealed that Alzheimer's patients, those with mild cognitive impairment, and cognitively unimpaired individuals could be differentiated based on plasma levels of free fatty acids and phospholipids. In the brain, DHA was reduced by 14% in phosphatidylserine phospholipids of the midfrontal cortex and by 12% in the superior temporal cortex. However, only in cognitively unimpaired individuals did DHA levels in the angular gyrus correlate with those in phosphatidylethanolamine [13].

In a dementia-free elderly population from the Framingham study, erythrocyte DHA was positively associated with brain volume, while the Omega-3 Index correlated with better visual memory, executive function, and abstract thinking, indicating a vascular pattern of cognitive impairment in individuals without overt dementia. Evidence of essential fatty acid deficiency in Alzheimer's brains includes elevated activity of stearoyl-CoA desaturase (which converts saturated fatty acids to monounsaturated fatty acids) and increased levels of monounsaturated and Mead acids, the latter being indicative of essential fatty acid deficiency. A significant negative correlation was observed between brain monounsaturated/saturated fatty acid ratios and cognitive performance, as measured by the Mini-Mental State Examination [14].

In a six-month trial involving 50 individuals over 65 years, participants were assigned to receive a placebo (linoleic acid), primarily EPA (1.67 g EPA + 0.16 g DHA), or primarily DHA (1.55 g DHA + 0.4 g EPA). Those receiving EPA or DHA showed improvements in Geriatric Depression Scores, while verbal fluency and self-reported physical health improved notably in the DHA group. [15]. These findings suggest EPA and DHA may alleviate depressive symptoms and reduce the risk of dementia progression. Similarly, supplementation with 900 mg/day of DHA improved verbal recognition memory but did not affect working memory or executive function. However, despite the association between brain DHA deficits and dietary or circulating DHA, interventional trials using EPA and DHA for Alzheimer's disease have not demonstrated consistent benefits [4].

There is strong evidence supporting the role of essential fatty acid abnormalities in depression. Despite variations in study designs, four independent meta-analyses of controlled trials involving patients with major depression and bipolar disorder have demonstrated significant benefits from n-3 fatty acid treatments. Major depression is anticipated to become the second leading cause of disability globally by 2020 [5].

Two systematic reviews highlight the importance of EPA and DHA in mood disorders[12]. Applying Sir Austin Bradford Hill's criteria for causality (strength, consistency, specificity, temporality, biological gradient, plausibility, coherence, experimental evidence, and analogy), depression and suicidality are closely associated with EPA and DHA levels. For instance, a study using EPA (1.2 g) and DHA (0.9 g) supplementation confirmed a reduction in suicidality. Additionally, studies on unipolar and bipolar disorders have documented deficits in n-3 fatty acids and elevated arachidonic acid/EPA or arachidonic acid/DHA ratios in serum, erythrocytes, adipose tissue, and brain phospholipids [4].

Significant correlations have been identified between plasma DHA levels and DHA content in erythrocytes and the nervous system. Among

cardiovascular risk factors, a low Omega-3 Index is associated with major depression and interleukin-6, a cytokine linked to major depressive disorder. Tissue deficits of EPA and DHA can result from inadequate intake or excessive dietary linoleic acid consumption [16].

A meta-analysis of 14 studies revealed that EPA, DHA, and total n-3 PUFAs (including alpha-linolenic acid, EPA, docosapentaenoic acid n-3, and DHA) were significantly lower in individuals with depression. Furthermore, a large meta-analysis evaluating the effects of EPA supplementation on depression found significant outcomes across doses ranging from 200 to 2200 mg [17].

A large meta-analysis on EPA supplementation for depression found that doses ranging from 200 to 2200 mg/day were effective in treating primary depression when EPA made up at least 60% of the EPA + DHA content. This finding was supported by another meta-analysis of randomized controlled trials [18]. In the 2005–2008 National Health and Nutrition Examination Survey, consuming any EPA + DHA was linked to fewer depressive symptoms. However, eating breaded fish, typically fried, was associated with a higher risk of severe depressive symptoms, as frying reduces EPA + DHA content.

Mechanistically, medication-free depressed individuals showed correlations between plasma DHA and arachidonic acid percentages with glucose metabolism rates in brain regions involved in depression [3]. While DHA plays significant roles in neuronal structure, resilience, and neuroprotection, dietary EPA is more strongly linked to antidepressant effects, despite its rapid disappearance from the central nervous system [19].

In elderly individuals with depression, a combination of EPA (1.67 g) and DHA (0.83 g) improved quality of life within two months. Among medical students, supplementation with EPA (2085 mg) and DHA (348 mg) over 12 weeks reduced anxiety and interleukin-6 levels. Adolescents with eating disorders and depression exhibited low EPA + DHA levels in erythrocytes, though nutritional rehabilitation alone improved their essential fatty acid (EFA) status without targeted intervention [3].

For bipolar depression, a meta-analysis demonstrated a moderate effect size (0.34) for n-3 fatty acid supplementation but found no significant benefits for mania. Erythrocyte DHA deficits were observed in both bipolar disorder and major depression, with some evidence pointing to peroxisomal dysfunction linked to DHA deficiencies. Mood stabilizers like lithium, valproic acid, and carbamazepine may work by reducing excessive arachidonic acid turnover [20].

Children with bipolar disorder showed no improvement in primary outcomes with flaxseed oil supplementation (up to 12 g/day). However, in secondary analyses, participants who achieved plasma EPA levels above 0.8% experienced significant symptom reductions. For pregnancy-related depression, a study of 14,541 women in southwest England found that EPA, docosapentaenoic acid n-3, and DHA intakes from seafood (0.2–0.41% of total energy or 445–917 mg/2000 calories) reduced maternal depression risk and improved neurodevelopmental outcomes in children [21].

However, a meta-analysis of 309 women with perinatal depression showed no overall benefit from n-3 supplementation, except in one small study where EPA (2.2 g) and DHA (1.2 g) were effective. Additionally, first-trimester dietary n-6/n-3 ratios exceeding 9:1 were associated with more than double the risk of postpartum depression [22].

Research has linked fatty acids to schizophrenia, revealing associations with semantic functions, polymorphisms in sterol regulatory element-binding proteins 1 and 2, abnormalities in anandamide (an endocannabinoid derived from arachidonic acid), and levels of circulating arachidonic acid and DHA. Chronic risperidone treatment has been shown to enhance DHA composition in rat

erythrocytes and prefrontal cortex, suggesting increased biosynthesis of DHA from α-linolenic acid. Similarly, a human study found that prefrontal essential fatty acid metabolism and erythrocyte membrane fatty acid composition improved with antipsychotic treatment, indicating enhanced essential fatty acid status and better membrane response predictability [23].

Erythrocyte analysis of 36 drug-free individuals with schizophrenia (compared to 36 controls) revealed low levels of arachidonic acid and DHA alongside a high n-6/n-3 ratio. These abnormalities normalized after three months of typical antipsychotic treatment, highlighting the critical roles of fatty acids in the development and treatment of schizophrenia. Supplementation with EPA (2000 mg/day) significantly improved Positive and Negative Syndrome Scale (PANSS) subscale scores in schizophrenia patients. In another study, perseverative errors decreased significantly at 24 weeks in patients taking 2 g of ethyl-EPA daily [3]. Furthermore, a double-blind, randomized controlled trial using EPA (700 mg) and DHA (480 mg) over 12 months reduced the risk of psychosis progression in young individuals with subthreshold psychotic symptoms [24].

Actions on Pregnancy and Lactation

Randomized controlled trials examining omega-3 fatty acid intake during low-risk pregnancies found no significant effects on gestational diabetes, preeclampsia, or hypertension. However, high omega-3 fatty acid consumption may slightly prolong pregnancy due to imbalanced prostaglandin production involved in childbirth. Fish oil supplementation during the third trimester can modestly extend pregnancy duration without impacting fetal growth or the labor process [25].

A meta-analysis of six randomized controlled trials showed that omega-3 supplementation in low-risk pregnancies increased the gestation period by an average of 1.6 days. In contrast, a 2007 meta-analysis found that while omega-3 fatty acids did not influence the gestation period in high-risk pregnancies, they could help reduce the risk of early premature birth [26].

Experts in the U.S. recommend that pregnant and lactating women consume at least 200 mg of DHA daily to support fetal and newborn development. Similarly, the European Food Safety Authority (EFSA) advises a daily intake of 100-200 mg DHA combined with 250 mg EPA for adults, including pregnant women [27].

During pregnancy and lactation, there is significant mobilization of polyunsaturated fatty acids (PUFAs) to support the development of fetal and infant tissues. A substantial portion of these PUFAs, particularly n-3 fatty acids, is utilized by the brain and nervous system, which are rich in these components. The essential fatty acid (EFA) requirement typically constitutes 3% of total caloric intake, increasing to 4.5% during pregnancy and 5-7% during lactation. Previous research has linked low birth weight to inadequate intake of linoleic acid (LA) and n-3 fatty acids [4].

In 1982, McNamara et al. documented the first reported case of human n-3 deficiency. The case involved a six-year-old girl who, after five months on a parenteral nutrition regimen deficient in alpha-linolenic acid (ALA), exhibited a 17% reduction in plasma docosahexaenoic acid (DHA) levels compared to her peers. She developed symptoms such as dermatitis, neurological issues (e.g., neuropathy and blurred vision), and psychological disturbances. These symptoms resolved when her parenteral nutrition was replaced with an ALA-enriched preparation [12].

Boys aged 6 to 12 years, both with and without attention deficit/hyperactivity disorder (ADHD), with lower plasma levels of total n-3 fatty acids exhibited more behavioural problems, learning difficulties, and health

issues than those with higher levels. Supplementation with n-3 fatty acids has been shown to reduce ADHD symptoms in both children with the condition and those with typical development [12].

Children with Autism Spectrum Disorders (ASD) have also been found to have lower n-3 levels compared to controls. Although the mechanisms underlying this association are not fully understood, the high concentration of DHA required by neural tissue highlights its importance for brain growth and development. However, the safety and efficacy of DHA supplementation as a medical treatment for ASD remain unproven [4].

Various inconsistent fatty acid abnormalities and theories related to autism have been reported, including findings from mouse studies linking maternal diets high in linoleic acid to autism. Although small double-blind, randomized controlled trials using EPA and DHA or arachidonic acid have shown some benefits, the evidence for the consistent effectiveness of these fatty acids in autism is lacking. Additionally, the absence of an accepted biomarker for autism, along with findings that suggest a greater environmental influence than previously thought, complicates the understanding of autism's full spectrum. Fatty acid analysis remains underutilized, which may lead to individuals with cognitive and social impairments due to abnormal fatty acid status being misclassified as autistic [28].

Children with attention-deficit hyperactivity disorder (ADHD) often exhibit low circulating levels of arachidonic acid, EPA, and DHA. Early intervention trials using various combinations of fatty acids produced inconclusive results. However, subsequent studies and a meta-analysis of 10 trials provided modest evidence of benefits, particularly in individuals with deficiencies and in children who did not respond to methylphenidate. Supplementation with DHA alone (600 mg from algal oil) over 16 weeks did not improve overall reading performance in 7- to 9-year-old children. Nevertheless, significant gains of approximately 20% and 50% were observed in subgroups with initial performance in the ≤20th and ≤10th percentiles, respectively, along with additional parent-reported behavioural improvements [29].

Actions on Eye

Some research suggests that essential fatty acid (EFA) intake may offer potential benefits for eye conditions such as dry eye syndrome, age-related macular degeneration (AMD), and cataracts. However, the evidence remains inconclusive, and further studies are necessary to draw definitive conclusions [30].

A randomized controlled trial on individuals with dry eye syndrome demonstrated that dietary supplementation with n-3 fatty acids alleviated symptoms and improved clinical markers associated with the condition. In an observational study, researchers found that consuming canned tuna or more than four servings of fish per week provided a protective effect against AMD. However, other oily fish known to be rich in EPA and DHA, such as sardines and mackerel, did not yield similar protective effects [31].

There is strong evidence suggesting that DHA influences both the risk and potential outcomes of traumatic brain injury (TBI). In a rat model, dietary DHA (1.2% of energy intake) was found to enhance brain-derived neurotrophic factor, which is associated with synaptic plasticity and cognition, and to stimulate synapsin I, which supports neuronal development, synaptic transmission, and neurite growth. It also activated cyclic adenosine monophosphate-responsive element-binding protein and the calcium/calmodulin-dependent kinase II signalling system, both crucial for learning and memory. In cases of psychological trauma, such as military-related or sports-related TBI, where low DHA levels are linked to increased suicide risk, emerging evidence highlights the prophylactic and therapeutic benefits of DHA. A daily intake of

up to 4 grams of fish oil is recommended for such cases [12].

Action on Gene Expression

Omega-3 and omega-6 fatty acids influence the expression of numerous genes involved in inflammation and immune responses by interacting with specific transcription factors such as peroxisome proliferator-activated receptors (PPARs). In some cases, polyunsaturated fatty acids (PUFAs) function similarly to steroid hormones by binding to receptors like PPARs, which then attach to gene promoters to regulate transcription. These fatty acids can also modulate transcription factors such as NFκB and Sterol Regulatory Element–binding Proteins (SREBP-1) within the cell nucleus. For instance, omega-3 fatty acids suppress NFκB activity, thereby reducing the expression of genes linked to inflammation, including those encoding eicosanoids and cytokines. Additionally, SREBP-1, which regulates the transcription of genes involved in the de novo synthesis of fatty acids, is inhibited by dietary omega-3 fatty acids, ultimately decreasing further synthesis of omega-3 fatty acids [12].

Action on Protein Biomolecules

Eicosanoids are bioactive lipid mediators, typically composed of 20-carbon hydrocarbon chains, that play a key role in regulating inflammatory and immune responses [4]. Dihomo-gamma-linolenic acid (DGLA), arachidonic acid (AA), and eicosapentaenoic acid (EPA) are released from cellular membranes in response to activation by hormones, cytokines, or other signals and serve as precursors for eicosanoid production. Eicosanoids derived from AA are considered more potent inducers of inflammation compared to those derived from EPA. Isoprostanes, on the other hand, are formed through the free radical-induced oxidation of polyunsaturated fatty acids (PUFAs). They act as markers of oxidative stress and exhibit both pro-inflammatory and anti-inflammatory properties [32].

Action on Rheumatoid Arthritis

Numerous meta-analyses and randomized controlled trials have indicated that polyunsaturated fatty acid (PUFA) intake can positively impact reducing the risk of rheumatoid arthritis, an autoimmune inflammatory disease affecting multiple joints and linked to cardiovascular conditions. PUFAs have been shown to decrease leukotriene B4, a pro-inflammatory marker, and improve blood profile levels by reducing triacylglycerol concentrations [33].

Actions on Behavioural Diseases

The high lipid content of neuronal tissue highlights the importance of fatty acids for brain function. Lipids make up approximately 60% of the human brain, with DHA accounting for 10% to 14% of the lipids in grey matter and smaller amounts in white matter. Together, DHA and arachidonic acid represent about 50% of the total fatty acids in neuronal membrane phospholipids. DHA crosses the blood-brain barrier efficiently and plays vital roles in neuron size, neurogenesis, neurite growth, synapse formation and function, neuronal integrity, brain gene expression, glucose transport, cognitive development, and learning ability. In contrast, EPA, α-linolenic acid, and docosapentaenoic acid (n-3) constitute only about 0.1% of the total brain fatty acids [34].

A deficiency in polyunsaturated fatty acids (PUFAs) and an imbalanced omega-3 to omega-6 fatty acid ratio have been linked to unipolar and bipolar disorders, as well as suicidal behaviour, according to recent epidemiological studies. While PUFA supplementation in patients with mental disorders showed a reduction in depression symptoms, no statistically significant differences were observed in omega-3 fatty acid levels between individuals with mental illness or suicidal behaviour and control groups [35].

Action on Cancer

Research has shown that omega-3 fatty acid intake may lower cancer risk due to their strong anti-inflammatory properties and their ability to inhibit cell growth factors. Recent studies suggest that higher omega-3 consumption or elevated blood levels of omega-3s are associated with a reduced risk of breast and colorectal cancers. However, conflicting evidence exists, as some studies have linked high omega-3 intake to an increased risk of prostate cancer, though these findings remain a subject of scientific debate [4].

Action on Diabetes

Plasma phospholipid analysis over a 10.6-year observation period indicates that higher concentrations of alpha-linolenic acid, EPA, and DHA are linked to a lower risk of type 2 diabetes in older adults. However, conflicting findings complicate the interpretation of the roles of linoleic acid, alpha-linolenic acid, EPA, and DHA in diabetes risk and management. For example, native Greenlanders exhibit a low prevalence of diabetes despite high rates of obesity and significant EPA and DHA intake. Similarly, dietary alpha-linolenic acid seems to protect Chinese Singaporeans from type 2 diabetes. Conversely, in people with diabetes, blood glucose levels show a slight positive association with EPA and DHA intake, and consuming two fish servings per day has been linked to an increased risk of developing type 2 diabetes [4].

Adding to the complexity, dietary linoleic acid is positively associated with diabetes risk, while plasma phospholipid linoleic acid is inversely related to it. Unlike rodent studies, human research suggests that supplementation with alpha-linolenic acid, EPA, or DHA does not improve insulin sensitivity. This discrepancy may be due to humans lacking peroxisome proliferator-activated receptor-alpha-regulated genes encoding enzymes like acyl-CoA oxidase, which limits the shift from lipogenesis to beta-oxidation in lipid metabolism. [36]. Furthermore, a recent meta-analysis found no significant association between fish, seafood, EPA, or DHA intake and the risk of developing type 2 diabetes. These findings imply that current levels of fish and fish oil consumption do not reduce diabetes risk and highlight the potential importance of dietary linoleic acid.

Action on Skin

Research is ongoing to understand how fatty acids contribute to the dermis and epidermis in forming protective barriers. While the full fatty acid cascade is absent in the skin, enzymes like cyclooxygenases 1 and 2 and lipoxygenases-5, -12, and -15 are expressed, suggesting potential for fatty acid-based interventions in certain skin conditions. For instance, oral EPA and DHA supplementation have been shown to increase the minimal erythema dose (MED) following ultraviolet radiation exposure. Two placebo-controlled studies (one with 1.8 g EPA and 1.2 g DHA, and another with 4 g purified EPA) demonstrated prolonged MED. Additionally, in cases of polymorphous light eruption, fish oil supplementation (1.8 g EPA and 1.2 g DHA) significantly reduced cutaneous prostaglandin E2 levels and increased MED after three months [37].

Action on Obesity

The rising prevalence of obesity-related health issues suggests that humans may adapt more effectively to nutrient scarcity than to abundance. Between 1909 and 1999, dietary linoleic acid intake from 273 food commodities showed a strong correlation with obesity ($r^2 = 0.68$, $P < 0.001$) and with key dietary sources like soybean oil ($r^2 = 0.83$, $P < 0.00001$), poultry ($r^2 = 0.94$, $P < 0.00001$), shortening ($r^2 = 0.86$, $P < 0.00002$), and sugar ($r^2 = 0.37$, $P < 0.04$). Notably, a reduction in physical labor during this period negatively correlated with obesity rates [38].

Obesity risk may originate before or during pregnancy, as inverse associations have been

identified between maternal EPA/DHA intake, maternal and umbilical cord plasma concentrations, and offspring skin-fold thickness at age three. Additionally, the linoleic acid content in human breast milk more than doubled between 1944 and 1990, while α-linolenic acid levels remained unchanged, promoting the synthesis of n-6 derivatives. Infant formula also shows elevated linoleic acid levels, ranging from 10% to 30%. In adults, even among those consuming a diet rich in olive oil, obesity and central fat distribution correlate positively with the linoleic acid content of adipose tissue and negatively with monounsaturated and α-linolenic acids [39]. This may be linked to increased synthesis of endocannabinoids, such as 2-arachidonoylglycerol and anandamide, from arachidonic acid.

Obesity also affects the immune system. Inflammatory gene expression is elevated in abdominal subcutaneous adipocytes and stromal vascular cells of obese versus non-obese individuals, as observed in Pima Indians [40]. Fatty acids influence this process, for instance, during an 8-week randomized trial comparing butter-rich and olive-oil-rich diets, saturated fatty acids increased the expression of approximately 1,500 immune-related genes, whereas oleic acid had a smaller or opposite effect on about 600 genes [4].

Sleep apnea, often linked to obesity, also shows associations with fatty acid profiles. In a study of 350 individuals undergoing sleep evaluations, the erythrocyte membrane DHA-to-total fatty acids ratio was inversely correlated with hypopnea severity, independent of fish oil supplementation or BMI. Each standard deviation increase in DHA levels was associated with a 50% reduced likelihood of severe obstructive sleep apnea [4].

Conclusion

Essential fatty acids (EFAs), including omega-3 and omega-6 fatty acids, are indispensable for numerous physiological processes and play a critical role in maintaining overall health. Among the omega-3 fatty acids, alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) are pivotal, with DHA and EPA being particularly important for brain function, cardiovascular health, and anti-inflammatory responses. Omega-6 fatty acids, such as linoleic acid and arachidonic acid, are essential for cellular structure, immune function, and inflammation regulation.

The diverse structural and functional roles of EFAs underscore their importance in various applications, ranging from clinical nutrition and dietary supplementation to therapeutic interventions for chronic diseases. Their influence extends to cellular membrane integrity, signaling pathways, gene regulation, and the synthesis of bioactive lipid mediators like resolvins and protectins. These molecules contribute to resolving inflammation, promoting neuronal survival, and supporting metabolic homeostasis.

Understanding the balance between omega-3 and omega-6 fatty acids in the diet is crucial, as an imbalance can lead to pro-inflammatory states associated with chronic diseases. The inclusion of dietary sources such as fatty fish, flaxseeds, and nuts, along with targeted supplementation when necessary, can help achieve optimal EFA levels.

As research continues to elucidate the complex roles of EFAs, their integration into personalized nutrition and medicine offers promising opportunities to enhance health outcomes. By leveraging their biochemical properties and therapeutic potential, EFAs remain a cornerstone of dietary science and clinical practice.

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