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The Role of Essential Fatty Acids in Human Health

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Abstract

Fatty acid research began about 90 years ago but intensified in recent years. Essential fatty acids (linoleic and α-linolenic) must come from diet. Other fatty acids may come from diet or may be synthesized. Fatty acids are major components of cell membrane structure, modulate gene transcription, function as cytokine precursors, and serve as energy sources in complex, interconnected systems. It is increasingly apparent that dietary fatty acids influence these vital functions and affect human health. While the strongest evidence for influence is found in cardiovascular disease and mental health, many additional conditions are affected. Problematic changes in the fatty acid composition of human diet have also taken place over the last century. This review summarizes current understanding of the pervasive roles of essential fatty acids and their metabolites in human health.

Keywords

arachidonic acid, eicosapentaenoic acid, EPA, docosahexaenoic acid (DHA), essential fatty acid,linoleic and α-linolenic

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Essential fatty acids are those necessary for biological function but must be obtained from dietary plant sources.

Humans require 2 such fatty acids: linoleic acid (C18:2n-6), an n-6 (ω-6) fatty acid with the first double bond 6 carbons from the methyl (non-acid) end; and α-linolenic acid (C18:3n-3), an n-3 (ω-3) fatty acid with the first double bond 3 carbons from the methyl end (chemically, linoleic is 9*Z*,12*Z*-octadecadienoic acid, with double bonds at the 9th and 12th carbons, and α-linolenic acid is 9*Z*,12*Z*,15*Z*-octadecatrienoic acid, with double bonds at the 9th, 12th, and 15th carbons; *Z* designating the *cis* position vs *E*, the *trans* position). Animals lack Δ-12 and Δ-15 desaturases necessary for synthesis of these 2 fatty acids.

The essential nature of certain fats was first demonstrated by Burr and Burr (1929), who observed dermatitis and impaired growth in rats fed a fat-free diet,[1] but their findings were rejected at the time.[2] In 1933, Hansen found that eczema in infants, then commonly fed skim milk and sucrose-based formulas, responded to topical lard applications, which contained linoleic and arachidonic acids.[1]

It was otherwise not possible to induce overt human essential-fatty-acid deficiency experimentally, and it did not appear until the development of total parenteral nutrition; the first preparations were fat free and capable of rapidly inducing deficiency. In 1969, a woman, within a month of receiving total parenteral nutrition, developed dermatitis resistant to topical corn oil (about 55% linoleic acid). She died 7 months later with profound n-6 and nearly complete n-3 deficiency in plasma, thus demonstrating the essentiality of both linoleic and α-linolenic acids. This conclusion was confirmed in 1970, when an infant who developed dermatitis after 3 months of fat-free total parenteral nutrition showed profound phospholipid n-6 and n-3 deficiencies in plasma and tissues at autopsy.[1]

In 1982, specific n-3 fatty acid deficiency was identified when 2 lipid emulsions became available for total parenteral nutrition, one made from safflower oil (high in linoleic but almost devoid of α-linolenic acids) and the other from soybean oil (moderate in linoleic and α-linolenic acids). A 6-year-old child, while receiving the safflower oil preparation, developed episodic numbness, tingling, weakness, impaired ambulation, leg pain, psychological disturbances, and blurred vision. Severe n-3 and moderate n-6 deficiencies were demonstrated. After switching to the soybean preparation, the neuropathy disappeared.[3]

Interest intensified after Bang, Dyerberg, and Nielsen, while investigating the very low incidence of cardiovascular disease and stroke among Greenland Inuits,[4] demonstrated that Inuits consuming n-3-rich diets had substantially different fatty acid profiles than Danes despite similar total dietary fat intake.[5-7] Lower prevalence of psoriasis, inflammatory bowel disease, asthma, rheumatoid arthritis, diabetes, and other autoimmune conditions was also found.[5]

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Subsequently, this complex burgeoning field has become important for human health. Ironically, evolutionarily unprecedented changes in human diets also began. In particular, linoleic acid intake has increased, and arachidonic, α-linolenic, eicosapentaenoic (EPA), and docosahexanaenoic acid (DHA) intakes have decreased, the study of which began only 3 decades ago.[8,9] Humans have adaptive mechanisms for deficiency states, but current dietary fatty acid practices appear to have created subtle maladaptive states. Current linoleic acid:α-linolenic acid intake ratios (up to 17:1 in the United States compared to 1:1 prior to 1900[10]) and limited EPA + DHA intakes represent a massive uncontrolled experiment with little supporting evidence of benefit but increasing evidence of harm.[11]

Essential Fatty Acids and Basic Research

Major efforts to identify all components of the plasma-based lipidome reveal almost 600 distinct molecular species from 6 lipid categories: fatty acyls, glycerolipids, glycerophospholipids, sphingolipids, sterol lipids, and prenol lipids.[12,13] Essential fatty acids are primarily found in the first 3 categories. Unfortunately, nonspecific designations such as "omega-6" and "omega-3" often hamper discussion of this field. Throughout this review, specific terminology will be used whenever possible. Also, this review will focus on human studies although animal studies have contributed immeasurably to this field.

Cell membranes are composed of large amounts of lipids, principally phospholipids made of 3-carbon glycerol backbones. The *sn*-1 (top carbon) position contains a saturated fatty acid, generally palmitic (C16:0), stearic (C18:0), or oleic acid (monounsaturated). Generally, the *sn*-2 (middle) position contains arachidonic acid, DHA, or linoleic acid. (One exception is breast milk, which places palmitic acid in *sn*-2 position.[14]) The *sn*-3 (lower) position contains phosphate moieties such as phosphatidic acid, phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine, or phosphatidylinositol.

Linoleic acid comprises about 20% of the fatty acids in human plasma phospholipids while α-linolenic acid contributes about 0.3%. In erythrocyte membranes, these fatty acids represent 9% and 0.03% of all fatty acids, respectively. Cardiolipin is a structurally unique phospholipid with 4 fatty acid residues, 60% to 80% of which are linoleic acid, and is a critical component of the electron transport system in the inner mitochondrial membrane.[15]

Linoleic acid has multiple potential metabolic fates, including the following: (*a*) β-oxidation, yielding acetyl-CoA for energy via the Krebs cycle; (*b*) sequential elongation to C26:2n-6; (*c*) desaturation and elongation to arachidonic acid, adrenic acid (C22:4n-6), and docosapentaenoic acid n-6 (C22:5n-6)[16,17]; (*d*) formation of products of oxidative stress, such as 4-hydroxynonenal and malonaldehyde; and (*e*) 9- and 13-hydroxy- and oxo-derivatives through the action of 12/15 lipoxygenase.[18,19] These metabolites undergo further modification. For example, arachidonic acid is the precursor of prostaglandins (mediators of pain responses), leukotrienes (inflammatory cytokines), thromboxane (potent mediators of cardiovascular disease), and endocannabinoids (in brain, modulators of inflammation, gut motility, temperature, appetite, obesity, and cardiovascular function[20]). Genotypic variants of 5-lipoxygenase act on arachidonic acid and show particular importance in cardiovascular disease.[21]

In contrast, α-linolenic acid predominately undergoes β-oxidation but is converted to EPA and then DHA via the same enzyme cascade used by linoleic acid (Figure 1).

Figure 1 illustrates this shared enzymatic cascade, with linoleic and α-linolenic acids competing on the basis of substrate availability.[9,22,23] Only 0% to 4% of ingested α-linolenic acid is converted to DHA.[24] Men seem to have a limited capacity to synthesize DHA.[24,25] When dietary linoleic acid is lowered from 10.5% of energy to 3.8% in healthy men but α-linolenic acid is kept constant (at 1%), EPA synthesis increases.[26] Incorporation of α-linolenic acid into tissue and conversion to DHA are related to the absolute amounts of dietary linoleic and α-linolenic acids rather than to their ratio (when the ratio was 19:1 vs 7:1).[27] When inadequate amounts of DHA are produced or there is a dietary deficiency, docosapentaenoic acid (n-6), a less-functional linoleic acid metabolite, is substituted in membranes,[16] reducing membrane fluidity and function. Thus, the importance of dietary EPA and DHA must be interpreted within the context of dietary linoleic acid.

Since arachidonic acid, EPA, and DHA also produce bioactive highly unsaturated fatty acid derivatives, they are also referred to as essential fatty acids. They form bioactive lipid mediators through cyclooxygenase, lipoxygenases, and cytochrome P-450 mechanisms.[17] In general, although the products of arachidonic acid are predominately inflammatory and n-3-derived metabolites are anti-inflammatory, the picture is more complex.[28]

Some dietary polyunsaturated fatty acids also function as ligands for nuclear receptors termed *adapted orphan receptors* and thereby affect gene transcription; α-linolenic acid is a weak regulator and EPA and DHA are strong regulators of hepatic gene expression.[29] These ligands include retinoid X-receptor and peroxisome proliferator-activated receptors-α, β, γ, and δ.[30] DHA activates retinoid X-receptors.[30] 4-Hydroxy-DHA (produced by 5-lipoxygenase) directly inhibits endothelial cell proliferation and sprouting angiogenesis via peroxisome proliferator-activated receptor-γ.[31] Neuroprotectin D1 (a dihydroxytriene derived from DHA) induces neuronal survival via secretase and peroxisome proliferator-activated receptor-γ-mediated mechanisms in Alzheimer disease models.[32] Peroxisome proliferator-activated receptor-α controls fatty acid oxidation[33,34] and induces Δ-5 and Δ-6 desaturases by stimulating sterol-regulatory element binding protein-1c.[35,36] The oxidative metabolite 13-hydroxy-linoleic acid (produced by the action of 15-lipoxygenase) activates peroxisome proliferator-activated receptor-γ by downregulating peroxisome proli ferator-activated receptor-β/δ.[37] Linoleic acid acts as an agonist for peroxisome proliferator-activated receptor-α/δ in upregulating osteoblast differentiation.[38]

For example, ingestion of a single saturated-fat shake transcriptionally upregulates genes but a DHA-enriched shake

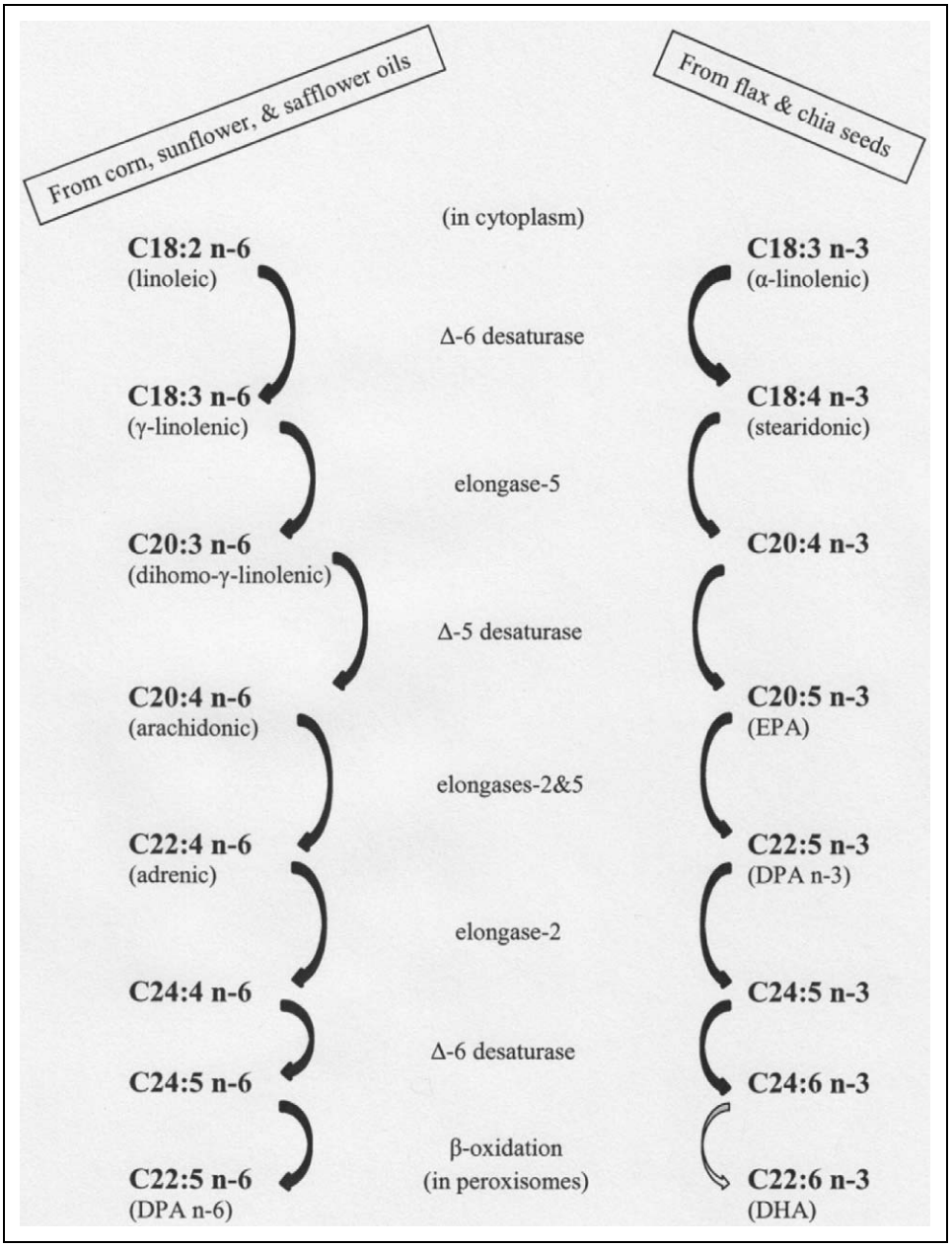

Figure 1. The cascade of linoleic and α-linoleic acids, primary sources, and shared enzymes.

downregulates the same genes.[39] Twenty-six weeks of consuming 1.8 g/day EPA + DHA results in upregulated expression of 1040 genes involved in inflammatory- and altered atherogenic-related pathways (eg, nuclear transcription factor kappa B-signaling, eicosanoid synthesis, scavenger receptor activity, adipogenesis, and hypoxia signaling), whereas high-oleate sunflower oil changes the expression of only 298 genes.[40] EPA and DHA upregulate peroxisome proliferator-activated receptor-α (which stimulates fatty acid oxidation and reduces triglycerides) and peroxisome proliferator-activated receptor-γ (which improves insulin sensitivity).[22]

The 6 double bonds in DHA enable it to assume more than 100 configurations.[41] DHA is both a structural molecule (constituting about 14% of brain fatty acids, mainly in synaptic membranes, dendrites, and photoreceptors[42,43]) and a precursor for hydroxylated forms called resolvins and protectins.[5] After seizure or brain injury, neuroprotectin D1, produced through 15-lipoxygenase-1, triggers signaling that sustains synaptic and circuit integrity, is anti-inflammatory, and induces cell survival.[43] DHA also appears to play a central role in the coordination of complex networks involving hepatic glucose, fatty acid, and amino acid metabolism to ensure efficient dietary protein utilization, especially in early development.[44]

EPA serves as precursor for E-resolvins (trihydroxylated molecules that are potent anti-inflammatory compounds)[5,45]

and DHA. In the central nervous system, EPA disappears through β-oxidation within minutes.[46,47]

Translation of human fatty acid metabolism into the clinical world presents significant challenges. (*a*) Human fatty acid metabolism differs fundamentally from animals and is magnified by human polymorphisms.[48] (*b*) Human intake estimates are approximations, making it difficult to demonstrate benefit in interventional or observational studies. (*c*) Isocaloric dietary alterations require substitution of carbohydrates, protein, or other fats; these inherently complicate interpretation. (*d*) Many diseases may be influenced by nutritional factors such as vitamin D_3[49] and, in Japan, taurine from fish.[50] (*e*) Biological optimals are still being differentiated from statistical norms. At present, tissue levels of EPA, docosapentaenoic acid n-3, and DHA, the closest determinants of risk, are considered to be most closely represented by those of modern Japan.[51] (*f*) While it is customary to express circulating concentrations as both mole percentages (ratios of total fatty acids) because of the high degree of interactivity of fatty acid molecules and less frequently as absolute values, the optimal mode of expression has not been agreed upon in all circumstances.

More fundamentally, there are differences between evidence-based medicine and evidence-based nutrition in humans.[52] The double-blind randomized placebo-controlled trial is evidence-based medicine's primary tool and is reliably used to assure drug efficacy. Drug trials are well suited for nondeficiency states (there being no drug-deficiency states), for dose-related and monotonic effects, for placebo comparisons, when clinical equipoise can be achieved, and when rapid effects are likely. In contrast, nutrient effects are observed in deficiency states (the creation of which is unethical in humans), are often polyvalent, may be hidden within biological noise, may be sigmoidal within a specific range, are not testable against a zero-intake group (unethical), may appear in concert with other nutrients,[53] and may not emerge for decades.[52] Cohort equipoise may be implausible or unethical. Consequently, nutrient trials tend simply to determine whether one level of nondeficient intake is better than another.[52] The extraordinary complexity of food makes it unlikely that randomized controlled trials will be conclusive.[54] In the complex field of fatty acids, the methods of evidence-based medicine may be appropriate in certain contexts, and elements of both approaches appear to be necessary.[52]

There is great promise that knowledge of fatty acid metabolism can be applied directly to human disease. In this report, we focus on those conditions with the strongest evidence but also point out conditions in which fatty acids are influential. The multiple roles of essential fatty acids in chronic disease risk reduction, a requirement of the current version of the Institute of Medicine's Dietary Reference Intakes, are apparent.[51,55]

Cardiovascular Disease

The evidence that EPA and DHA prevent cardiovascular disease is particularly strong.[28,56] Improvement in modifiable risk factors such as blood pressure, platelet reactivity, thrombosis, circulating triglyceride concentrations, vascular reactivity, cardiac arrhythmia (and the risk of sudden cardiac death[57]), heart-rate variability, and inflammation have been shown.[22] The precise mechanisms-of-action relating to EPA and DHA are still being established but converge on membrane phospholipids, especially cardiac membranes.[15,57] In animals, DHA increases cardiolipin membrane content and reduces mitochondrial permeability transition pore opening, an action that reduces cell death via apoptosis or necrosis.[15] Consistent with these findings, trained healthy cyclists undergoing exercise to exhaustion and taking fish oil 8 g/day for 8 weeks had lower heart rate, whole-body oxygen consumption, and rate-pressure product (with no change in time-to-fatigue), indicating increased oxygen utilization.[58] Cardiac cytochrome P450 enzymes accept EPA and DHA as alternative substrates, producing potent antiarrhythmic n-3-epoxyeicosanoids.[59] In humans, moderate wine intake itself appears to have a dose-related fish-like effect on EPA and DHA concentrations in both low- and high-α-linolenic-acid intakes, even after adjusting for confounding factors.[60]

Epidemiologically, coronary heart disease mortality between Japanese, Icelandic, South Korean, and American men is inversely reflected in serum EPA and DHA.[61] Similarly, circulating DHA correlates inversely with carotid intima-media thickness, a measure of endovascular inflammation.[62] In addition, a carotid intima-media thickness study shows that people with 5-lipoxygenase genotypic variants (found in black—20.4%, Asians or Pacific Islander—19.4%, Latino—3.6%, and non-Latino white subjects—3.1%) are at greater risk for cardiovascular disease when arachidonic and linoleic acids are ingested. Increased dietary EPA and DHA blunt these risks.[63]

Supplementation with various combinations of EPA, DHA, and α-linolenic acid reduce both morbidity and mortality. While the largest 2 secondary-prevention studies, GISSI-Prevenzione ($n > 11\,000$; 900 mg EPA + DHA/day)[64] and JELIS (Japan EPA Lipid Intervention Study; $n > 18\,000$; EPA 1.8 g/day)[65] show clear benefit, their findings are corroborated by a review of 46 studies using strict criteria for study design and specific attention to EPA + DHA intakes.[66]

Predictive biomarkers are emerging. Sudden cardiac-arrest risk in people older than 65 years was much higher when 2 products of de novo lipogenesis (C18:1n-7, *cis*-vaccenic acid, an end-product of excessive endogenous fatty acid synthesis, and C16:1n-9) were elevated.[67] In people who underwent elective percutaneous coronary intervention, the serum EPA/arachidonic-acid ratio was inversely associated with risk of adverse coronary events, including cardiac death.[68]

Other specific predictive fatty acid ratios are being developed, including the Omega-3 Index and the n-3/n-6 ratio. The Omega-3 Index is well standardized,[69] reflects long-term EPA + DHA status,[69] and correlates closely with myocardial essential-fatty-acid composition.[70] The Index is derived from erythrocyte membrane phospholipid composition by adding % EPA + % DHA, and in cross-cultural studies, predicts cardiac death and reduces acute coronary syndrome risk.[69] It is a better than the Framingham Risk Score[71] or other standard risk factors.[72] An Omega-3 Index <4% is associated with increased

cardiovascular disease risk, and the optimal Omega-3 Index is >8%.[71] The Index increases about 0.24% for every 4 g dietary EPA + DHA/month.[69] A 24-center dietary analysis of post–myocardial infarction patients revealed that fish intake, older age, non-white race, and EPA + DHA supplementation were associated with higher Omega-3 Index, but frequent fast-food intake, smoking, and diabetes mellitus with a lower Index.[73] A large body of evidence, from epidemiology, prospective studies, case–control investigations, meta-analyses of randomized n-3 interventional trials, and studies comparing the Omega-3 Index in depressed versus nondepressed cardiac patients supports the hypothesis that EPA and DHA deficiency is a preventable risk factor for both conditions.[74]

The n-3/n-6 ratio combines one n-9, three n-3, and four n-6 fatty acids and correlates highly with the percentage of n-6 fatty acids in tissue ($r = .73$, $P < .0000$).[75,76] Tissue n-6 correlates well with risk of death from cardiovascular disease.[77] Food composition data from the US Department of Agriculture Nutrient Database (which incorporates 11 crucial n-3 and n-6 fatty acids[78]) combined with data from the n-3/n-6 blood test yields predictive tissue responses; a practical Omega 3-6 Balance Food Score guide to simplify food choices among 5100 foods has been developed.[75]

The Mediterranean diet is associated with reduced cardiovascular disease risk.[79] Enhanced EPA and DHA status are found in Mediterranean-diet adherents.[80,81] Dyslipidemic people in Spain have prominent inverse associations between carotid intima-media thickness and both serum DHA and oleic acid (C18:1).[82] Significant associations were found between brain magnetic resonance imaging white-matter hyperintensity volume (a marker of brain small-vessel damage) and components of the Mediterranean diet such as the ratio of dietary monounsaturated-to-saturated fat, an independent predictor of cardiovascular disease risk and cognitive impairment.[83] Various explanations for the benefits of the Mediterranean diet have been proposed, including high polyphenol content, high oleic acid content (from olive oil), lower linoleic acid composition (about 7 g or 4.6% of energy[84]), high vegetable and fish composition, and a reasonable α-linolenic acid content. (Adulteration of olive oils with linoleic-containing oils is common.) Intriguingly, diets in Japan are low in monounsaturated fatty acids,[85] yet the incidence of cardiovascular disease is low.[86]

Although no role for dietary α-linolenic acid was found in a MEDLINE search for prospective cohort studies and randomized trials, the effects of relatively low α-linolenic intakes may have been obscured by high linoleic acid intakes.[87] Large studies demonstrate that dietary α-linolenic acid (mean intake 0.74-0.82 g/day) was inversely associated with rate-adjusted QT interval, a risk factor for sudden death,[88] and with calcified atherosclerotic plaque in the coronary arteries as determined by cardiac computerized tomography, even when fish intake was low.[89]

Fish oil does not suppress some inflammatory markers. It may actually increase low-density lipoprotein concentrations[90] while lowering plasma triglycerides. By suppressing adipose tissue inflammation, fish oil reduces intracellular lipolysis and thereby lowers circulating free fatty acids. In contrast, fish oil increases β-oxidation in extracellular adipose tissue, heart, and skeletal muscle and lowers fatty acid delivery to the liver.[91]

The GISSI-Heart Failure study showed reduced mortality and hospital admission for cardiovascular reasons in people with chronic heart failure already receiving recommended therapy when given 850 to 882 mg combined EPA + DHA (as ethyl esters in 1.2:1 ratio) per day.[92] Risk reduction appeared to be due to antiarrhythmic effects. Low C20:4 n-3 (eicosatetraenoic acid, an EPA precursor) and high C18:1 n-7 (*cis*-vaccenic acid) have been associated with significantly higher mortality in chronic heart failure.[93] Fish consumption in a large meta-analysis (n = 176 441) is associated with modest reduction in heart failure risk.[94] Risk factors such as systolic blood pressure and carotid intima-media thickness are reduced by consumption of tuna, baked fish, and broiled fish but are raised by fried fish.[95] Theoretically, EPA + DHA may reduce mitochondrial-permeability-transition-pore opening and thereby prevent apoptosis-inducing leakage of calcium into mitochondria followed by cell death.[15] EPA + DHA (human equivalent dose 5.1 g/day) in rats prevents pressure-induced ventricular dilatation.[96]

Although a meta-analysis and recent studies found little evidence that dietary EPA and DHA reduce atrial fibrillation risk,[97,98] a 10-year study showed risk to be positively associated with plasma free fatty acids.[99] A large prospective analysis of plasma phospholipids showed graded and inverse associations between atrial fibrillation incidence and combined EPA + docosapentaenoic acid n-3 + DHA and DHA alone.[100] A subsequent meta-analysis confirmed that long-chain n-3 polyunsaturated fatty acids given after cardioversion provide no benefit. However, recurrence risk is lower when given at least 4 weeks prior to cardioversion.[101]

A small but inverse relationship between blood pressure and dietary α-linolenic acid, EPA, and DHA has been demonstrated in mechanism-of-action studies in animals models[102] and was confirmed in normotensive, prehypertensive, and untreated hypertensive people.[103] Interventional trials ranging from 1 g fish oil to 15 to 40 g/day ground flaxseed (largely α-linolenic acid) reduce blood pressure by small but measurable amounts in chronic renal, postmenopausal, obese, and dyslipidemic patients.[102]

Design flaws and the application of medical evidence-based methodologies to nutritional studies complicate the interpretation of some studies.[98,104,105] Concerns include the very small size of studies (with disproportionally greater weights given to smaller studies), short study duration, and inappropriate exclusion of some trials.[106] More recent trials[104,107,108] were either underpowered,[98] underdosed,[98,104] had delayed entry after myocardial events,[98,104] or lacked power due to fewer cardiovascular events than originally anticipated.[107] Also, they were conducted among patients receiving more statins, angiotensin-converting-enzyme inhibitors, and other cardiovascular medications that likely obscured the benefits of fish oil supplementation. Moreover, cardiac drugs themselves appear to alter important fatty acid concentrations.[109,110] The composite

evidence from multiple sources is that modest EPA + DHA consumption reduces cardiovascular disease mortality.[28]

In summary, current evidence strongly supports the roles of fatty acids, particularly EPA, DHA, and α-linolenic, in reducing the risk of cardiovascular disease. There is noteworthy evidence supporting their roles in heart failure, hypertension, and atrial fibrillation as well.

Mental Health

The high lipid content of neuronal tissue implicates fatty acids as critical for brain function. The total lipid content of human brain is about 60%[111] with DHA about 10% to 14% of lipids in grey matter and with less in white matter.[42,112] DHA and arachidonic acid together constitute about 50% of the total fatty acids in neuronal membrane phospholipids.[42] DHA readily crosses the blood–brain barrier and plays critical roles in "neuron size, neurogenesis, neurite growth, synapse formation and function, neuronal integrity, gene expression in the brain, glucose transport, cognitive development, and learning ability."[113] EPA, α-linolenic acid, and docosapentaenoic acid (n-3) comprise only about 0.1% of total brain fatty acids.[114]

Depression

The evidence for essential fatty acid abnormalities in depression is strong. Despite design variations, 4 independent meta-analyses of controlled trials in patients with major depression and bipolar disorder found significant benefit from n-3 fatty acid treatment.[115-118] Major depression is projected to become the second most important cause of disability worldwide by 2020.[119]

Two systematic reviews support the role of EPA and DHA in mood disorders.[120,121] Using Sir Austin Bradford Hill's criteria relating evidence to causality (strength, consistency, specificity, temporality, biological gradient, plausibility, coherence, experimental evidence, and analogy),[122] depression and suicidality are closely linked to EPA and DHA status within each realm.[123,124] Reduced suicidality was confirmed in a trial using EPA 1.2 g + DHA 0.9 g.[125] N-3 fatty acid deficits and/or elevated serum, erythrocyte, adipose, and brain phospholipid arachidonic acid/EPA or arachidonic acid/DHA ratios have been shown in a number of studies of unipolar and bipolar disorders.[126] Many investigators have found significant correlations between plasma DHA content and DHA in erythrocytes and nervous system.[127] Among cardiovascular risk factors, low Omega-3 Index is associated with major depression and interleukin-6,[128] which is known to be associated with major depressive disorder.[129] EPA + DHA tissue deficits can be caused by low EPA + DHA intakes or by excessive dietary linoleic acid.

A meta-analysis of 14 studies showed that EPA, DHA, and total n-3 PUFA (α-linolenic acid, EPA, docosapentaenoic acid n-3, plus DHA) were significantly lower in depressed people.[114] A large meta-analysis of the effects of EPA supplementation on depression concluded that in the 200 to 2200 mg/day range those supplements in which EPA was ≥60% of EPA + DHA were effective against primary depression[130]; this conclusion was confirmed by another meta-analysis of randomized controlled trials.[131] In the 2005-2008 National Health and Nutrition Examination Survey, ingestion of any EPA + DHA was associated with fewer depressive symptoms. However, consumption of breaded fish was associated with increased risk of severe depressive symptoms because breaded fish is generally fried and frying lowers EPA + DHA content.[132] Mechanistically, medication-free depressed subjects show that plasma DHA % and arachidonic acid % correlate with relative rates of glucose metabolism in areas implicated in the neurocircuitry of depression.[133] Although DHA has major roles in structure, neuronal resilience, neuroprotection, and volume,[134] dietary EPA correlates better with antidepressant effect than does dietary DHA even though EPA disappears rapidly from the central nervous system.[47]

Depressed elderly adults experienced improved quality-of-life within 2 months on EPA (1.67 g) + DHA (0.83 g).[135] N-3 fatty acid supplementation (EPA 2085 mg + DHA 348 mg/day) reduced anxiety and lowered interleukin-6 in 68 medical students over 12 weeks.[136] In 217 adolescents with eating disorders and depression, low EPA + DHA proportions were found in erythrocytes.[137] Nutritional rehabilitation alone, however, improved their EFA status, apparently without the need for specific EFA intervention.[138]

Bipolar depression also appears to benefit from n-3 fatty acids according to a meta-analysis of n-3 fatty acids studies ($P = .029$) but not for mania ($P = .099$) with moderate effect size (0.34) and no significant likelihood of publication bias.[139] Erythrocyte DHA deficits were identified in bipolar disorder as well as major depression.[140] Other findings implicate peroxisomal dysfunction due to DHA deficits. Mood stabilizers, such as lithium, valproic acid, and carbamazepine, appear to exert their effect by reducing excessive turnover of arachidonic acid.[141]

Children with bipolar disorder show no benefit in primary outcomes when given flax seed oil (gradually raised to 12 g/day).[126] However, clinician-rated Global Symptom Severity correlated inversely with total plasma % α-linolenic acid, % EPA, and positively with the n-6 fatty acids, arachidonic acid, and docosapentaenoic acid n-6. In a secondary analysis, those individuals able to attain plasma EPA > 0.8% (8 of 34 subjects) had significant reduction in overall severity.[126]

In pregnancy-related depression, a recent study of 14 541 pregnant women in southwest England concluded that EPA, docosapentaenoic acid n-3, and DHA intakes from seafood ranging from 0.2 to 0.41 en% (percent of total energy), or 445 to 917 mg/2000 calories, reduced risk of maternal depression and adverse neurodevelopmental outcomes in children among 97.5% of a population in which linoleic acid is 4 to 6 en%.[124] A meta-analysis of 309 women (303 on placebo) with perinatal depression did not show benefit except for one small study in which EPA 2.2 g + DHA 1.2 g were given.[142,143] First-trimester dietary n-6/n-3 ratios greater than 9:1 have been associated with more than twice the risk of subsequent postpartum depression.[144]

Schizophrenia

Links have been established between fatty acids and schizophrenia demonstrating associations with semantics,[145] sterol regulatory element-binding protein 1 and 2 polymorphisms,[146] anandamide (an arachidonic acid-derived endocannabinoid) abnormalities,[147,148] and circulating arachidonic acid and DHA.[149] A novel mechanism-of-action has been shown in which chronic risperidone treatment increases rat erythrocyte and prefrontal cortex DHA composition indicating significant augmentation of α-linolenic acid-to-DHA biosynthesis.[150] Indeed, a human study shows linkage between prefrontal essential fatty acid metabolism, erythrocyte membrane fatty acid composition, and improvement in function with antipsychotic treatment, implying that improvement is through enhancement of essential fatty acid status as well as membrane-based response predictability.[151] Erythrocyte analysis in 36 drug-free people with schizophrenia (vs 36 controls) showed low arachidonic acid and DHA but an elevated n-6/n-3 ratio. After 3 months of typical antipsychotic drug treatment, these abnormalities normalized, consistent with crucial roles of fatty acids in both the etiology and treatment of schizophrenia.[149] Significant improvement in Positive-and-Negative-Schizophrenia Score subscale results were found using EPA (2000 mg/day) in people with schizophrenia.[152,153] Perseverative errors, as measured by the Wisconsin Card Sort Test, declined significantly at 24 weeks in 27 patients who received 2 g ethyl-EPA/day.[154] A double-blind randomized controlled trial using EPA 700 mg + DHA 480 mg (over 12 months) reduced the risk of progression of psychosis in young people with subthreshold psychotic states.[155]

Dementia

Epidemiologic studies link fish intake to dementia.[156] Decreased fish and fish oil consumption in noncarriers of ApoE ε4[157] and low plasma DHA[158] have been associated with Alzheimer disease as well as impaired memory, cognition, and mood in people older than 65 years with depression.[159] Postmortem analyses of 3 brain cortical regions show that patients with Alzheimer disease, mild cognitive impairment, or no cognitive impairment can be identified on the basis of plasma free fatty acids and phospholipids. In brain, DHA was 14% lower only in phosphatidylserine-containing phospholipids of the midfrontal cortex and 12% lower in superior temporal cortex. Only in those with no impairment, however, did % DHA correlate with % DHA in the phosphatidylethanolamine of the angular gyrus.[160] In a dementia-free Framingham elderly population, erythrocyte DHA correlated with brain volume, and the Omega-3 Index correlated directly with visual memory, executive function, and abstract-thinking scores, all suggesting a "vascular" pattern of cognitive impairment in people with no overt evidence of dementia.[161] Essential fatty acid deficiency in the brains of people with Alzheimer disease is further documented by the finding that elevated stearoyl-CoA desaturase activity (converts palmitic [C16:0] to palmitoleic [C16:1] acid and stearic [C18:0] to oleic [C18:1] acid[162]) was present along with elevated mono-unsaturated and Mead acids (elevation of the latter defines essential fatty acid deficiency). A prominent negative correlation between brain monounsaturated/saturated fatty acid ratios and measures of cognition, such as the Mini Mental State Examination, was also found.[163]

Among 50 people aged >65 years, a 6-month trial divided into placebo (linoleic acid 2.2 g), primarily EPA (1.67 g + DHA 0.16 g), or primarily DHA (1.55 g + EPA 0.4 g) showed that Geriatric Depression Scores improved in those receiving either EPA or DHA, and verbal fluency and self-reported physical health improved in those primarily receiving DHA. This study suggests that EPA and DHA may reduce depressive symptoms and the risk of progression to dementia.[164] Similarly, DHA (900 mg/day) resulted in improved verbal-recognition-memory scores but not working memory or executive function.[165]

Nevertheless, it is puzzling that Alzheimer-specific interventional trials using EPA and DHA have not been clearly beneficial in spite of known brain DHA deficits and the close association between dietary and circulating DHA.[166]

Gender, Age, and Cognition

Despite the relative difficulty of DHA synthesis among males versus females, differences in brain composition or epidemiology may not be seen. However, in the Third National Health and Nutrition Examination Survey (1988-1994) with analysis of multiple biological, social, and environmental risk factors in more than 4000 children aged 6 to 16, the only dietary factors related to cognitive performance were n-3 and n-6 fatty acids. In both male and female children, dietary n-3 fatty acid intake correlated positively with cognitive test scores. Female children showed twice the correlation as males, even exceeding the negative effects of lead exposure. In female children, the correlation of test scores with dietary n-6 fatty acids was negative.[113]

In healthy adults, dietary EPA + DHA are associated with cortico-limbic gray matter volumes (anterior cingulate cortex, amygdala, and hippocampus), areas supporting emotional arousal and regulation, which may be related to observed effects on memory, mood, and affect.[167]

Attention-Deficit Hyperactivity Disorder (ADHD)

Children with attention-deficit hyperactivity disorder often have low circulating concentrations of arachidonic acid, EPA, and DHA, although initial interventional trials using a variety of combinations of fatty acids yielded inconclusive results.[168,169] Subsequent trials and a 10-trial meta-analysis provide modest evidence of benefit in deficient individuals and in methylphenidate-refractory children.[170-174] DHA alone (600 mg, from algal oil) given to 7- to 9-year-old children over 16 weeks did not change reading performance overall. However, gains around 20% and 50% were seen in the subgroups whose initial performance was in the ≤20th and ≤10th centiles, respectively, with additional improvements in parent-reported behavior.[175]

Autism

A variety of inconsistent fatty acid abnormalities and plausible theories of autism, including a maternal diet high in linoleic acid in mice,[176] have been reported.[177-180] Although small double-blind randomized controlled trials using EPA + DHA[181,182] and arachidonic acid[183] have shown benefit, there is no consistent evidence of benefit from administration of these fatty acids.[184] It must also be acknowledged that, since there is no accepted biomarker for autism, recent study demonstrates greater degrees of environmental influence than previously suspected,[185] its full spectrum is still being defined, and fatty acid analysis is underutilized. Consequently, individuals with cognitive and social impairments due to abnormal fatty acid status may be misclassified as autistic.

Brain Trauma

A strong case can be made for the influence of DHA in the risk and, possibly, the outcome of traumatic brain injury. In a rat model, dietary DHA (1.2% energy) enhances brain-derived neurotrophic factor, which is linked to synaptic plasticity and cognition, and stimulates synapsin I, which plays an important role in neuronal development, synaptic transmission, and neurite outgrowth; cyclic adenosine monophosphate-responsive element-binding protein, involved in learning and memory; and the calcium/calmodulin-dependent kinase II signaling system, required for learning and memory.[186] In the context of psychological insults, as occurs in military- (in which low DHA status is a significant factor in suicidal death[187]) and sports-related traumatic brain injury, there is emerging evidence of the benefits of DHA for prophylaxis and treatment. Up to 4 grams of fish oil per day is recommended.[188]

Other Dysfunctional Mental States

Fourth-year university students to whom DHA-rich fish oil was administered (DHA 1500-1700 mg + EPA 201-241 mg/day) appeared to experience less outwardly directed aggressive ideation under conditions of mental stress (final exams)[189] than under nonstressed conditions.[190]

In people with substance abuse, a small study (n = 35) provided evidence that those with higher DHA levels were less likely to relapse,[191] and challenges using *d*,*l*-fenfluramine, a serotonin probe allowing functional assessment of hypothalamic 5-hydroxytryptophan responses, correlated with DHA and EPA status in cocaine-abusing men.[192] Significant DHA depletion has been observed in men with pedophilia and is hypothesized to interfere with the impulse control and aggression-hostility common in this condition.[193] A 20-fold higher risk of homicide ($r = .94$, $P < .0001$) was associated with high dietary linoleic acid consumption between 1960 and 2000 in 5 industrialized countries,[194] findings subsequently replicated in several additional countries (Unpublished, personal communication with author).

In summary, while the strongest evidence favors the importance of EPA and DHA for depression, essential fatty acids have emerged as being crucial for many aspects of brain dysfunction.

Additional Conditions

Cancer

There are theoretical bases for suspecting a relationship between cancer and fatty acids, especially considering the influences of fatty acids on inflammation.[195] Arachidonic acid is the sole precursor of lipid inflammation-related mediators (eicosanoids) produced by enzymes such as cyclooxygenases, lipoxygenases, and cytochrome P450 enzymes. Approved drugs that inhibit arachidonic acid derivatives, such as aspirin and selective cyclooxygenase-2 inhibitors, not only block cytokine-related pain but also suppress tumor growth experimentally[196] and in human epidemiology.[195,196] Up to 40% of the fatty acid composition of cancer cell membranes is arachidonic acid.[197] In mice, a Western-style diet increases colonic tumor risk by activating tumor necrosis factor-α, prostaglandin E2, nuclear factor-κB, and Wnt inflammatory pathways in macrophages.[198]

Dietary histories show that breast cancer risk is positively associated with n-6 intake in premenopausal women and inversely with n-3 intake in obese women.[199] Women with certain 5-lipoxygenase-activating protein polymorphisms whose dietary linoleic acid intake is above 17.4 g/day have increased breast cancer risk.[200] Large studies in Sweden[201] and France[202] show interactions between heterocyclic amine content as well as food sources of linoleic and α-linolenic acids in breast cancer risk. Similarly, postmenopausal Chinese women in Singapore who have null genotypes for specific glutathione S-transferases have about 30% lower risk of breast cancer based on marine n-3 fatty acid intake.[203]

Epidemiologic studies of prostate cancer largely focus on fish intake and have been equivocal although methodological problems hamper study. Metastatic risk, however, shows more definite inverse associations with dietary fish intake, especially among men with specific cyclooxygenase-2 polymorphisms, DHA being a potent cyclooxygenase-2 inhibitor.[204,205]

A double-blind experiment (n = 40) in people with non-small-cell lung cancer using EPA 2.02 g + DHA 0.92 g for 8 weeks showed higher functional and quality-of-life status.[206] A trial in a similar population using EPA 510 mg + DHA 340 mg was associated with improved body weight and reactive oxygen species status during chemotherapy.[207]

Oxidative Stress and Inflammation

Plasmalogens are oxygen-ether-linked molecules with C16:0, C18:0, or C18:1 at the *sn*-1 position next to highly reactive arachidonic acid or DHA at the *sn*-2 position in the phospholipid molecule. They may protect against oxidative stress and function as terminators of free radical damage.[208] Plasmalogens constitute about 15% to 20% of cell membrane phospholipids.[208]

Chronic overproduction of pro-inflammatory mediators may have adverse effects in certain conditions. EPA and DHA inhibit these effects.[22] Immunomodulatory activities of EPA and DHA are complex and include modification of lipid mediator responses, such as reduction in arachidonate-derived cytokines and increasing synthesis of resolvins via cyclooxygenases and lipoxygenases; phagocytosis enhancement; inhibition of T-cell proliferation; and expression of major histocompatibility complexes I and II.[209] Linoleic acid increases monocyte chemotaxis and adhesion to human aortic endothelial cells.[210] Interleukin-1β, interleukin-1α, and tumor necrosis factor-α can be suppressed by high-dose fish oil (18 g/day) in 6 weeks (n = 9).[211] Superoxide dismutase activity and plasma glutathione (a major antioxidant) increased in elderly patients taking fish oil 2 g/day exposed to particulate matter.[212]

Interleukin-18, an independent cardiovascular disease risk factor, correlated inversely with serum EPA and DHA in high-risk elderly men given 2.4 g/day EPA + DHA.[213] An 8-week randomized controlled trial in healthy middle-aged men using EPA 1.8 g+ DHA 0.3 g/day found that only the plasma soluble intercellular adhesion molecule modified cardiovascular risk.[214] High EPA + DHA intake (1.8 g total) changed the expression of 1040 genes in mononuclear cells, including those involved in nuclear factor-κB and eicosanoid synthesis in healthy elderly Dutch men.[40] In exercise-trained men, 2224 mg EPA + 2208 mg DHA reduced C-reactive protein and tumor necrosis factor-α over 6 months.[215] Several inflammatory markers, including high-sensitivity C-reactive protein, fell in 6 months in dyslipidemic patients.[216] However, 3.5 g/day fish oil did not change a number of serum cytokines, chemokines, or cell adhesion molecules in healthy middle-aged Dutch men.[217] Thai children (n = 94) taking 200 mg EPA + 1000 mg DHA for 6 months had increased plasma phosphatidylcholine and fewer, shorter upper respiratory infections but no changes in plasma interleukin-2 receptor, interleukin-10, or interleukin-6.[218]

Contrary to the expectation that highly unsaturated molecules would increase oxidative stress, fish oil (1.25 or 2.5 g; EPA/DHA ratio 7:1) for 4 months decreased F2-isoprostane[219] and interleukin-6.[220] In the context of psychological stress, structural equation modeling of the influences of erythrocyte DHA, arachidonic acid, and pro-inflammatory cytokines (interleukin-1, interleukin-6, and tumor-necrosis factor) on perceived-stress-scale coping demonstrate that the benefits of DHA are largely direct effects unrelated to the effects of these cytokines.[221] On the other hand, arachidonic acid had a negative effect on coping skills and was partially mediated via increased pro-inflammatory cytokine production.[221]

Despite these observations and significant basic research supporting its existence, a consistent relationship between EPA + DHA, inflammatory markers, and oxidative stress in humans has been elusive. Vitamin D status may confound these efforts since it fluctuates seasonally and modulates some of the same cytokines such as interleukin 1β, interleukin-6, interleukin-10, tumor necrosis factor-α, interferon-γ, as well as T-cell numbers and phenotypes.[222,223]

Arthritis

Suppression of arachidonate-derived eicosanoids, such as prostaglandin E_2, appears to require higher EPA + DHA doses (EPA at least 2.7 g/day).[224] Miles and Calder systematically reviewed all available randomized controlled trials using EPA or DHA in rheumatoid arthritis, of which 23 met criteria for review; almost all reported some clinical improvement. Low-dose studies (<1.5 g EPA + DHA/day; n = 3) reported no benefits.[224] In a large study (n = 472) using magnetic resonance imaging, an inverse relationship between total n-3, as well as DHA, and patellofemoral cartilage loss was found. In addition, there was a positive association between plasma arachidonic acid and synovitis, these findings being consistent with diet-related influences on osteoarthritis.[225] Long-term fish oil ingestion reduces expression of leukocyte inflammatory genes and decreases cytokine production of stimulated leukocytes, which would likely benefit inflammatory diseases such as rheumatoid arthritis.[33] In juvenile idiopathic arthritis, fish oil (2 g/day) for 12 weeks dramatically improved clinical response and reduced nonsteroidal anti-inflammatory drug use, interleukin-1, and tumor necrosis factor-α.[226] A separate meta-analysis of 17 randomized controlled trials using fish, seal, or krill oil (and one using flaxseed oil) showed significant benefit for inflammatory joint pain associated with rheumatoid arthritis, as well as inflammatory bowel disease and dysmenorrhea.[227]

Diabetes

Plasma phospholipid analysis reveals that, during observations for 10.6 years, higher α-linolenic acid, EPA, and DHA concentrations are associated with lower risk of type 2 diabetes mellitus in older people.[228] However, paradoxical observations confound the interpretation of role of linoleic acid, α-linolenic acid, EPA, and DHA in diabetes risk and management. On the one hand, native Greenlanders, despite a high prevalence of obesity and high EPA + DHA intake, have little diabetes,[229] and dietary α-linolenic acid appears to protect Chinese Singaporeans from type 2 diabetes.[230] On the other hand, in diabetics, blood glucose is positively associated (minimally) with EPA and DHA intakes,[231] and ≥2 fish servings/day is associated with increased risk of developing type 2 diabetes.[232] In a seeming paradox, dietary linoleic acid was positively but plasma phospholipid linoleic acid was inversely associated with type 2 diabetes risk in humans.[233] In contrast to rodents, human studies suggest that administration of neither α-linolenic acid, EPA, nor DHA improves insulin sensitivity.[234] These species differences may be explained by human lack of peroxisome proliferator-activated receptor-α-regulated genes encoding enzymes such as acyl-CoA oxidase resulting in less ability to shift lipid homeostasis toward β-oxidation rather than lipogenesis.[102] A recent meta-analysis revealed no association between the risk of developing type 2 diabetes and fish, seafood, EPA, or DHA intake.[235] These studies suggest that, with regard to n-3 fatty acid intake, current levels of fish and fish oil supplementation do not reduce risk and that dietary linoleic acid may be an important factor.

Infancy

Many biological factors led to widespread DHA and arachidonic acid supplementation of infant formulas about 10 years ago. A variety of observations led to the conclusion that breast-milk DHA composition should be replicated in infant formulas, including the finding that bottle-fed infants dying of nonneurological events had 10% to 30% lower central nervous system DHA than breast-fed infants.[236] The addition of DHA (0.1% energy) and arachidonic acid (0.43% energy) to infant formula improves visual acuity.[237,238] DHA- (0.36% energy) and arachidonic acid- (0.72% energy) supplemented formulas (concentrations comparable to breast milk) were associated with improvement in means-end problem solving at age 9 months.[239] Cognitive function was better at 18 months when formulas contained DHA (0.32% energy) and arachidonic acid (at 0.64% energy).[240] Infants with specific single nucleotide polymorphisms of the gene encoding Δ-6 desaturase appear to explain, at least in part, the cognitive benefit from breastfeeding.[48] In 11 875 children, Hibbeln found that, after adjustment of 28 potential confounding variables, maternal consumption of less than 340 g seafood per week was independently associated with the child being in the lowest quartile for verbal intelligence.[241]

Despite these studies, Bayley Scale–based meta-analyses do not confirm that infant cognition is affected.[242,243] However, this test was designed to detect delays and, considering the dynamic nature of development in infancy, may not be suited for assessment of cognitive achievement.[243]

Aging

Older, hospitalized women are prone to essential fatty acid deficiency. A small group of hospitalized French women had low DHA, linoleic acid, and monounsaturated fatty acids but high fatty acids associated with increased cardiovascular risk. About one third ingested fewer than 3 g of linoleic acid per day, and 86% ingested less than 0.5% energy as α-linoleic acid.[244] In patients with coronary heart disease, the Omega-3 Index varies inversely with the rate of telomere shortening, an indirect measure of aging and chronic oxidative stress.[245] Sedentary overweight middle-aged and older adults given fish oil (1.25 and 2.5 g; EPA/DHA ratio 7:1) resulted in increased telomere length as the n-6/n-3 ratio declined.[219]

Skin

The mechanisms by which fatty acids support the dermis and epidermis in creating barriers is being explored. Although the entire fatty acid cascade is not present in the skin, cyclooxygenases 1 and 2 and lipoxygenases-5, -12, and-15 are expressed, creating the potential for intervention with fatty acids in some dermatological conditions. Specifically, oral EPA + DHA raise the minimal erythema dose following exposure to ultraviolet radiation. Two placebo-controlled trials (one using 1.8 g EPA + 1.2 g DHA and one using 4 g purified EPA) showed minimal erythema dose prolongation.[246,247] In polymorphous light eruption fish oil (1.8 g EPA + 1.2 g DHA) dramatically reduced cutaneous prostaglandin E_2 production and increased minimal erythema dose after 3 months.[248]

Obesity

The current wave of obesity-related health conditions demonstrates that humans appear to adapt better to nutrient deprivation than to abundance. From 1909 to 1999, total dietary linoleic acid from 273 food commodities correlated highly with obesity ($r^2 = .68$, $P < .001$) and with primary dietary linoleic acid sources: soybean oil ($r^2 = .83$, $P < .00001$), poultry ($r^2 = .94$, $P < .00001$), shortening ($r^2 = .86$, $P < .00002$), and sugar ($r^2 = .37$, $P < .04$).[249] (Of course, a shift away from physical labor correlated negatively with obesity.) Obesity may start before or during pregnancy since prominent inverse associations were found between maternal EPA + DHA intake, maternal plasma concentrations, and umbilical cord plasma concentrations and skin-fold thickness in offspring at age 3 years.[250] The linoleic acid composition of human breast milk more than doubled from 1944 to 1990, while α-linoleic has remained constant, favoring synthesis of n-6 derivatives. The linoleic acid composition of infant formulas has also increased, ranging from 10% to 30%.[251] In human adults, even those consuming a high olive oil diet, the degree of obesity, and central distribution of body fat correlates with the linoleic acid content of adipose tissue and correlates negatively with monounsaturated and α-linoleic acids.[252] The underlying mechanism may involve enhanced synthesis of the endocannabinoids—2-arachidonoylglycerol and anandamide—from arachidonic acid.[249]

The immune system is well known to be affected in obesity. There is increased expression of inflammation-related genes in abdominal subcutaneous adipocytes[253] and preadipocytes/stomal vascular cells[254] isolated from obese versus nonobese Pima Indians. Fatty acids appear to play a role. During an 8-week randomized controlled trial in humans using a butter-rich versus an olive-oil-rich diet, adipose tissue differences in transcriptosome-mediated expression of immune-related genes were observed. Saturated fatty acids primarily increased the expression of around 1500 immune-function genes but oleic acid had a smaller or opposite effect on about 600 genes.[33]

Sleep apnea is commonly thought to be associated with obesity. However, the erythrocyte membrane DHA/total fatty acids ratio was inversely associated with hypopnea in 350 people undergoing sleep studies, with no relationship to fish oil supplementation or body mass index. For each 1 standard deviation increase in DHA level, there was a 50% lower likelihood of being classified as having severe obstructive sleep apnea.[255]

The Role of Linoleic Acid

Cardiovascular disease has been designated the index disease for assessing optimal linoleic acid intake and thus for recommending current high linoleic intakes (at least 5% to 10% energy[256]). Interestingly, reexamination of this recommendation indicates the need for caution because earlier

interventional studies usually did not separate n-3 from n-6 fatty acids or define chain length (linoleic vs α-linoleic ± EPA + DHA). When these studies were more recently separated into mixed n-3 + linoleic acid versus specific linoleic acid trials, cardiovascular disease outcomes were no better in linoleic acid trials and may actually have been worse.[257,258] The benefits of a diet high in polyunsaturated fatty acids may have been due to n-3 fatty acids rather than linoleic acid.

The mechanism by which linoleic acid is reputed to lower risk is its known low-density lipoprotein cholesterol lowering effects, which are indirect indicators of cardiovascular disease risk.[259] However, there is otherwise little basic knowledge of possible mechanisms. Indeed, low-density lipoprotein receptor protein expression, considered to be a favorable hallmark of low-density lipoprotein catabolism,[260] while upregulated by EPA, DHA, and arachidonic acid, is unaffected by linoleic, α-linoleic, or oleic acids.[261] Consequently, noncardiac aspects of human health must also be examined.

Regarding brain composition, there is evidence in developing piglets that high dietary linoleic acid inhibits brain-neurite DHA accretion and that less functional docosapentaenoic acid (n-6) is substituted in cortical neurons.[16] Conversely, lowering linoleic intake from 10.5% energy to 3.8% in middle-age men, while keeping α-linoleic intake at 1% energy, resulted in increased EPA but no change in arachidonic acid. This confirms that the linoleic acid requirements for arachidonic acid synthesis are less than 3.8% energy.[262] In addition, oxidized metabolites of linoleic acid, which are more than 50 times more concentrated than arachidonic acid derivatives such as prostanoids and isoprostanes, have the potential to adversely affect disease processes including chronic pain, Alzheimer dementia, coronary heart disease, and nonalcoholic steatosis. These metabolites fall significantly when dietary linoleic acid is lowered from 6.7% to 2.4% of energy in humans.[19]

A wide range of conditions appear to be associated with excessive dietary linoleic acid. The risk of gastroschisis increases with higher dietary linoleic acid.[263] A 10-year study showed that the risk of age-related macular degeneration was lowest in those consuming the lowest amounts of linoleic acid.[264] The dietary n-6/n-3 ratio highly correlates with neovascular age-related macular degeneration.[265] One-third greater risk of cholelithiasis among men was observed at autopsy following a 1959-1968 interventional trial in which the experimental group received vegetable oils for two-thirds of the animal fat in 40% fat diets.[266] Linoleic acid consumption has been linked to the risk of ulcerative colitis[267] and is consistent with high linoleic acid in erythrocyte phospholipids,[268] high arachidonic acid content of adipose tissue,[269] as well as circulating prostaglandin E_2 and leukotriene B4 in these patients.[270] Plausible evidence has been presented linking excessive dietary linoleic acid to nonalcoholic fatty liver disease.[271] Some cancers, such as scirrhous gastric cancer, may be more prone to progression by high linoleic acid intake through suppression of angiostatin, which results in increased angiogenesis,[272] an essential element of malignancy. Higher erythrocyte total n-6 polyunsaturated fatty acids, as well as downstream linoleic metabolites dihomo-γ-linolenic, arachidonic, and docosapentaenoic (n-6), predict depressive symptoms in people, and lower docosapentaenoic acid (n-3) is associated with more self-reported body pain in people older than 65 years.[159] Increased rates of depression and decreased age of onset for those born 1930-1940 paralleled increases in linoleic acid intake.[273]

Certain contexts exhibit unexplained low circulating linoleic acid concentrations despite adequate linoleic acid intake. These include cystic fibrosis, in which the problem is independent of absorption and nutritional status,[274,275] nonalcoholic steatohepatitis,[276] eating disorders and weight loss,[137] and profound intellectual disabilities with paralysis.[277,278] Increasing dietary linoleic acid in the cystic fibrosis animal model merely increased arachidonic acid–derived inflammatory cytokines.[279] The clinical significance of these observations is not yet known.

Safety

Hibbeln concluded that, at seafood intakes greater than 340 g/week during pregnancy, the risks of nutrient insufficiency from a low-seafood diet far outweigh the risks of trace-element contamination.[241] This is in contrast to some recommendations regarding high consumption (≥5 servings/week) in which specific guidelines for pregnant women regarding mercury intake have been presented.[280] EPA + DHA at 900 mg/day from seafood during pregnancy was adequate to meet the neurodevelopmental requirements of the fetus and prevent maternal depression.[124] Although frequent fish consumption is the ideal, many people cannot meet optimal recommendations so fish oil supplements are needed. Supplements contain no mercury, which is protein-bound, and contain low amounts of dioxins and polychlorinated biphenyls.[28]

In 1523 post–myocardial infarction patients, the Omega-3 Index was not associated with increased bleeding risk.[281] Although the original studies among Greenland-Inuit people revealed long bleeding times and a tendency to bleed at their customary high levels on intake,[282] 9 human studies (1.0-6.0 g EPA + DHA) found no significant effects on bleeding time, platelet aggregation, platelet activating factor, prothombin formation, or abnormal surgical bleeding.[188]

Intravenously, 3-day infusions of a fish oil emulsion resulted in a significant shift toward n-3s in peripheral blood monocyte phospholipids (n = 8) but no evidence of cytokine stimulation or oxidative stress.[283] Conversely, oral oxidized fish oil (1.6 g EPA + DHA) did not result in increased markers of oxidative stress, lipid peroxidation, or inflammation.[284]

Current Recommendations

Estimates of Paleolithic diets from a variety of foraging settings found low average linoleic acid intakes (2.3% to 3.6% energy; 2.54-8.84 g/day) and high average α-linoleic acid intakes (3.7% to 4.7% energy), with monounsaturated fatty acids 5.6% to 18.5% energy and saturated fatty acids 11.4%

to 12% energy. Compared with Western diets, Paleolithic diets were lower in linoleic acid but higher in protein.[53]

The current recommendation for primary cardiovascular disease prevention, at minimum, is 250 mg/day EPA + DHA (combined) or at least 2 servings of oily fish/week.[285] The American Heart Association recommendations are based on known coronary heart disease risk status: people with no documented coronary heart disease should eat oily fish at least twice weekly (about 450 mg EPA + DHA[286]), people with known coronary heart disease should take 1 g EPA + DHA/day, and people who want to lower triglycerides should take 2 to 4 g/day.[286,287] The American College of Cardiology has similar recommendations.[28] The Food and Agricultural Organization of the United Nations guidelines are similar but recommend no more than 3 g EPA + DHA/day.[288] Anchovy, Atlantic herring, and both farmed and wild salmon contain, in decreasing order, 2055 to 1840 mg/100 g EPA + DHA, and Atlantic mackerel, bluefish, Atlantic sardines, and trout contain from 1203 to 936 mg/100 g.[28] Current daily DHA intake in the United States is estimated to be 70 mg, in Australia 90 mg, in Germany 170 mg, and in France 250 mg.[41]

The US Institute of Medicine recommends that linoleic acid intake should be 14 to 17 g/day for men and 11 to 12 g for women (5% to 10% energy), with α-linoleic acid intake 1.6 g/day for men and 1.1 g/day for women (0.6% to 1.2% energy) but offers no specific recommendations for EPA or DHA.[55] Current α-linoleic acid intakes range from 0.5 to 2 g/day, and linoleic-acid intakes are 5- to 20-fold higher.[22]

In mental health, emerging evidence brings into question the justifiability of basing EPA + DHA recommendations on coronary heart disease prevention alone. An analysis of epidemiologic (including 60-fold cross-national differences in prevalence rates of major depression and bipolar disorder, being the lowest in Asia countries), dietary, interventional trial data, and Omega-3 Index differences suggests that correction of DHA deficiency has the potential to dramatically alter the risk of recurrent affective disorders.[119] Although cultural differences may influence diagnostic criteria for psychiatric conditions, it has been shown that in order to reduce mental illness risk to that of traditional Japan, daily DHA intake (as EPA + DHA) is estimated to be 400 to 700 mg/day for children, 700 to 1000 mg/day for adults, and 1000 to 1500 mg/day for established affective disorders, with the optimal EPA:DHA ratio 2:1.[119]

Recommendations must also be driven by context: current EPA + DHA intake, linoleic acid status (current intake and body stores), risk factors such as hypertriglyceridemia, coronary heart disease history, underlying health conditions, and, broadly, mental health history. In particular, dietary allowance for EPA + DHA depends on intakes of linoleic, α-linoleic, and arachidonic acids. Current intakes in the United States require as much as 3600 mg EPA + docosapentaenoic acid (C22:5n-3) + DHA for optimal health, that is, to achieve an optimal level of 60% of tissue long-chain fatty acids as n-3 fatty acids.[51] In the Philippines, where linoleic acid intakes are about 0.8% energy, only about 275 mg of these n-3 fatty acids are required.

Table 1. Linoleic and α-Linolenic Acid Composition (%) of Common Oils.[a]

	Linoleic	α-Linolenic
Corn	53.5	1.2
Soybean	51.0	6.8
Canola	20.3	9.3
Flax seed	14.3	53.4
Chia seeds	5.8	17.8
Safflower		
Cooking oil	74.6	0
High oleate	12.7	0.01
Sunflower	65.7	0
Walnut	52.9	10.4

[a]From National Nutrient Database for Standard Reference, 2012; Release 24.[78]

Reducing linoleic acid intake to 2% energy would decrease long-chain n-3 fatty acid requirements by 90%,[51] and lowering dietary linoleic acid from 8% energy to 1% energy raises tissue EPA + DHA concentrations 10-fold.[124] The International Society for the Study of Fatty Acids and Lipids recommends 500 mg EPA + DHA in the context of linoleic acid as 2% energy and α-linoleic acid as 0.7% energy.[51]

Table 1 displays average linoleic and α-linoleic acid content of common oils. A 1-page table of n-6 and n-3 content of common foods is also available.[51]

Concluding Comments

Since the pioneering work of Burr and Burr, the important roles of fatty acids have been progressively recognized. However, many questions remain. While it is overly simplistic to characterize EPA and DHA as panaceas, it would also be tragic to misrepresent or undervalue the role of these and other fatty acids in human health.

General concerns have emerged. Nonspecific terminology, such as "PUFA" and "HUFA," cause confusion, making specific terminology increasingly necessary.[289] Differences in fatty acid metabolism between animals and humans should be acknowledged and placed in context.[290] Advances in the definition, identification, clarification, and dissemination of the clinical impact of fatty acid abnormalities in individuals is necessary. In psychiatry and cardiovascular disease, the responsibility for "food as medicine" has not been embraced by any particular health care discipline and, unfortunately, has been subtly avoided, creating gaps in the provision of useful complementary care related to fatty acids.[291,292]

A number of seed-oil-producing plants have been modified to increase oleic acid content.[293] Because of concern for dwindling fish oil supplies, efforts have been directed toward development of soybean oils with higher stearidonic acid (C18:4 n-3), which is more efficiently converted to EPA than is α-linoleic acid.[294] While stearidonic acid is more efficient at raising erythrocyte membrane EPA, it is not as efficient as EPA administration itself[295,296] and, unfortunately, does not

alter erythrocyte DHA.[297] The clinical benefits of plant-oil-derived stearidonic acid have not yet been clarified.

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