REVIEW ARTICLE

Polyunsaturated Fatty Acids: Impact on Health and Disease Status

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ABSTRACT

Over the last decades, the polyunsaturated fatty acids (PUFAs) have been largely explored not only for their nutritional value but also for the numerous biological functions and therapeutic effects. The serum and erythrocyte levels of PUFAs depend on the genetic control of metabolism as well as the dietary intake and are considered to reflect the health and disease status of an individual. Two families of PUFAs, omega-3 (*n*-3) and omega-6 (*n*-6), have gained much attention because of their involvement in the production of bioactive lipid mediators and therefore, a balanced omega-6/omega-3 ratio is crucial in maintaining the overall health of an individual. Omega-3 PUFAs, notably eicosapentaenoic acid (EPA, 20:5*n*−3) and docosahexaenoic acid (DHA, 22:6*n*−3) have been shown to exert beneficial effects, possibly due to their lipid-lowering, anti-inflammatory, anti-hypertensive and cardioprotective effects, whereas omega-6 fatty acids such as arachidonic acid (ARA, 20:4*n*−6) exhibit the opposite properties. Even though, numerous epidemiological studies and clinical interventions have clearly established the effectiveness of omega-3 PUFAs in various pathological conditions including dyslipidemia, obesity, diabetes, cancer, cardiovascular and neurodegenerative diseases, some controversies do exist about the beneficial effects of omega-3 PUFAs and need to be clarified. Larger clinical trials with extended follow-up periods are required along with a careful dose selection, in order to confirm the clinical significance and efficacy of omega-3 PUFAs as therapeutic agents.

Key Words: *Cardiovascular Diseases, Docosahexaenoic Acid, Disease, Polyunsaturated Fatty Acids, Health.*

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Introduction

Lipids are small non-polar biological molecules which perform diverse functions in a cell. Lipids serve as the main source of energy (9 kcal/mol), compared to proteins and carbohydrates (4.5 kcal/mol) and form a major structural constituent of biological membranes. The simplest lipids are the fatty acids that contain a carboxyl group (COOH) attached to a hydrocarbon chain with a terminal methyl group. Most of the naturally occurring fatty acids have an even number of carbon atoms and linear hydrocarbon chains, except for some exceptions in bacteria which have branched or cyclic structures.[1] Moreover, fatty acids are further classified based on the absence or presence of one or more double bonds into saturated or mono-/poly-unsaturated fatty acids respectively. Polyunsaturated fatty acids (PUFAs) of interest include omega-3 (*n*-3) and omega-6 (*n*-6), depending on the position of the first double bond at third or sixth carbon atom from the methyl end of the fatty acids. The long-chain polyunsaturated fatty acids (LC-PUFAs) from the omega-3 and omega-6 families are derived from their respective precursors, namely, α-linolenic acid (ALA; C18:3*n*-3) and linoleic acid (LA; C18:2*n*-6). ALA and LA are essential fatty acids that mammals have very limited capacity to synthesize and therefore can only be obtained from the diet.

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Dietary sources of PUFAs

Studies have shown that human populations around the world may have different capacities to synthesize LC-PUFAs from plant-based medium chain PUFAs, due to the variations in the fatty acid desaturase (FADS) gene cluster.[2] In humans, ALA is converted into eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) at the approximate rates of 8-20% and 0.5-9%, respectively.[3] Furthermore, diet is considered as one of the

important factors to modify the human capacity to synthesize LC-PUFAs from their respective precursors.[4] Therefore, a continuous supply in the diet is very important to ensure whole-body LC-PUFAs content.

Omega-3 PUFAs can be obtained from fish (e.g., salmon, mackerel, sardines, pollock, bluefish, and black cod), walnuts, flax seeds, linseeds and green leafy vegetables such as purslane and spinach, while omega-6 fatty acids are mainly obtained from vegetable oils such as soybean, safflower, sunflower and corn oil.[5]

Although fish is the primary source for health-promoting omega-3 PUFAs, the biggest challenge is to achieve their sustainable production due to decreasing global fish stocks as well as the safety issues related to environmental pollutants. Therefore, there has been considerable interest in the last few decades to produce omega-3 PUFAs from alternative sources such as marine bacteria and microalgae.[6,7] However, in order to overcome the low productivity of PUFAs using these organisms, various metabolic engineering strategies have been employed to optimize the biosynthetic pathways of PUFAs with the ultimate objective to achieve a successful industrial-scale production.[8,9]

Biosynthesis of long-chain omega-3 and omega-6 fatty acids

The biosynthesis of LC-PUFAs is a process that takes place primarily in liver. However, the efficiency of these processes is low (less than 0.5%) in humans and is influenced by ALA and LA intake and various pathological conditions.[10,11]

In liver, dietary precursors ALA and LA are converted into EPA or arachidonic acid (ARA) respectively via different steps involving desaturation by Δ6 FADS (encoded by FADS2 gene), chain elongation by very long chain fatty acids (ELOVL) protein 5, further desaturation by Δ5 desaturase (encoded by *FADS1* gene) (Figure 1). Two successive elongations of EPA by ELOVL5 & 2 and a desaturation by Δ6-desaturase produces tetracosahexaenoic acid (24:6*n*-3) in endoplasmic reticulum (ER).

In mammals, DHA production from 24:6*n*-3 involves the peroxisomal β-oxidation through the successive actions of acyl-coenzyme A oxidases, D-bifunctional protein and peroxisomal thiolases, referred to as 'Sprecher's shunt'.[12,13] DHA is then transported back to ER[14,15] to be incorporated into membrane phospholipids by esterification or the deacylation-reacylation reaction. These translocations between ER and peroxisomes are supposed to be responsible in part for the low efficiency of DHA biosynthesis in mammals.

In addition, omega-3 and omega-6 PUFAs can be further metabolized into eicosanoids by the action of cyclooxygenases and lipoxygenases to produce different series of biologically-active molecules such as prostaglandins, thromboxanes, leukotrienes, 5-hydroxy-eicosatetraenoic acids and lipoxins (Figure 1).[16] Interestingly, the omega-6 PUFAs-derived eicosanoids are important mediators of inflammation and atherogenesis, whereas the eicosanoids produced from omega-3 PUFAs (prostanoids, docosanoids and neuroprotectins) possess anti-inflammatory, anti-oxidative, immunoregulatory, vasodilatory and neuroprotective properties.[17] Therefore, an imbalance in the production of these eicosanoids may lead to the development of various pathophysiological conditions.

The omega-6/omega-3 ratio and dietary recommendations

The omega-6/omega-3 ratio in the diet is of crucial importance in predicting and maintaining the overall health of an individual. Our ancestral diets were found to be enriched with omega-3 fatty acids and therefore a balanced omega-6/omega-3 ratio. However, the shift from omega-3 fatty acids towards high amounts of saturated fatty acids and omega-6 fatty acids has perturbed the omega-6/omega-3 balance from 1:1 to 10-20:1 in modern Western diets.[18] This has consequently led to an increased prevalence of various inflammation-related chronic diseases such as cancer, inflammatory bowel disease, rheumatoid arthritis and cardiovascular and neurodegenerative diseases.[19] The recommended dose of EPA+DHA in the diet ranges from 40 to 250 mg per day for infants older than six months as well as for children and adolescents, however, 250 to 1000 mg per day has been recommended for adults.[20,21]

PUFAs as predictors of health and diseased status

The implication of omega-3 and omega-6 fatty acids

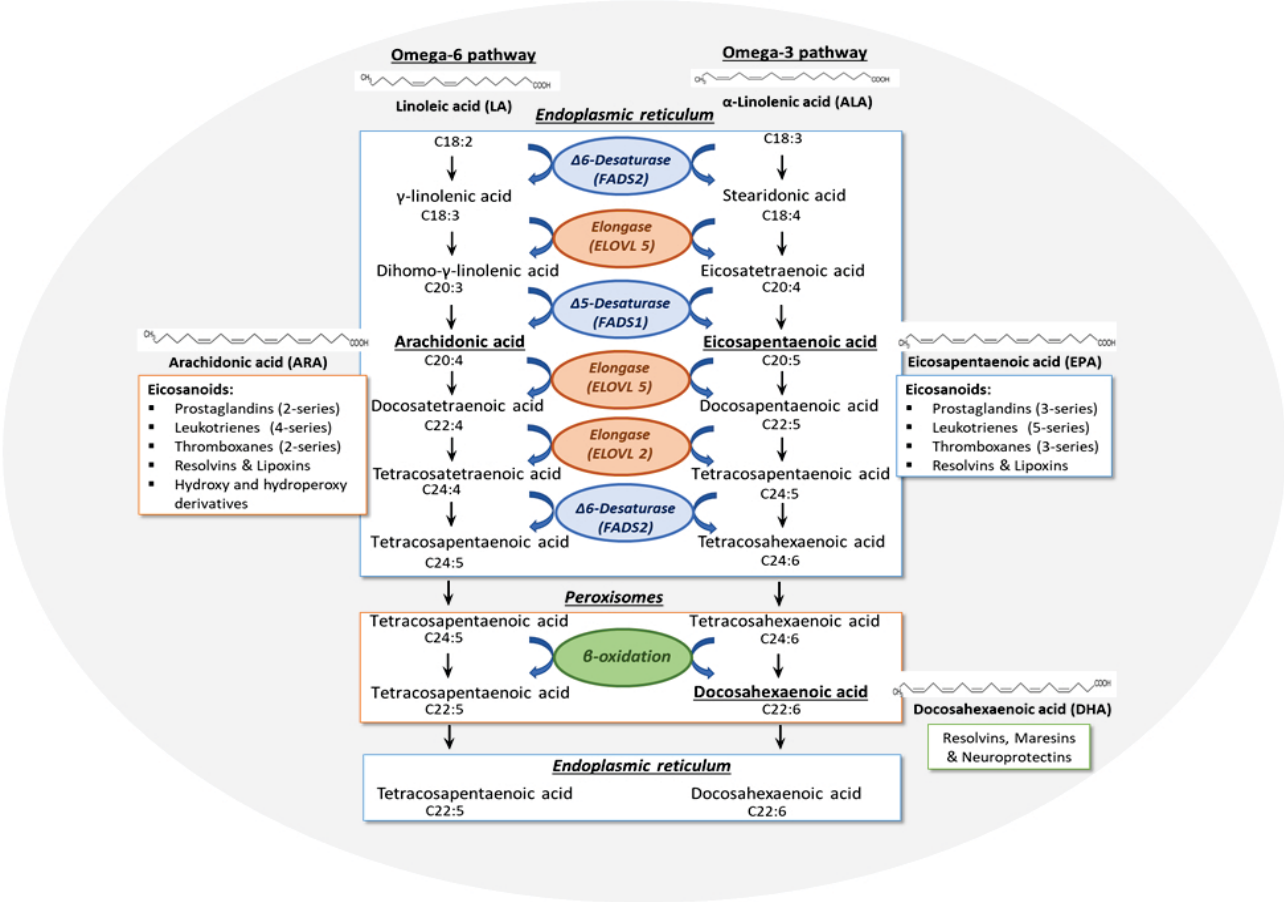

Fig 1: Biosynthesis of long-chain omega-3 and omega-6 fatty acids in mammals

Biosynthesis of long-chain omega-3 and omega-6 fatty acids involves a cascade of desaturation-elongation reactions in endoplasmic reticulum to produce arachidonic acid (ARA; C20:4n-6) from linoleic acid (LA; C18:2n-6). The conversion of α-linolenic acid (ALA; C18:3n-3) into eicosapentaenoic acid (EPA; C20:5n-3) and docosahexaenoic acid (DHA; C22:6n-3) occurs in endoplasmic reticulum and/or peroxisomes. The LC-PUFAs thus produced, are further metabolized to produce signaling molecules which are implicated in various anti-inflammatory or pro-inflammatory processes.

in human health and disease has been increasingly reported in the last few decades. Unlike omega-6 PUFAs, a large body of evidence has supported the beneficial roles of omega-3 PUFAs in various pathophysiological conditions including metabolic syndrome, cardiovascular diseases, cancer, depression, and neurodegenerative illnesses (Figure 2).

Omega-3 PUFAs have also been shown to function against inflammation and oxidative stress, which are underlying causes of different disorders. Several mechanisms may be involved in mediating the effects of fatty acids, including modifications in the physicochemical properties and functions of biological membrane, control in expression of genes, receptors and associated proteins, or the production of metabolites.[22] Moreover, the erythrocyte levels of PUFAs (omega-3 index) have been shown to be strongly correlated with the PUFAs enrichment in different organs, thereby reflecting an individual's health condition.[1] Nevertheless, the findings that illustrate the opposite or no effects of these PUFAs in different groups of patients with various pathologies should also be taken into consideration, in order to devise meaningful therapeutic strategies to improve health and prevent diseases.

Metabolic syndrome

Metabolic syndrome (MetS) is a complex disorder which refers to a clustering of three or more interrelated conditions including hypertension, dyslipidemia (high triglycerides and low HDL levels), abdominal obesity and impaired glucose tolerance.[23] A large body of evidence has revealed the patients with MetS as predictors of diabetes and

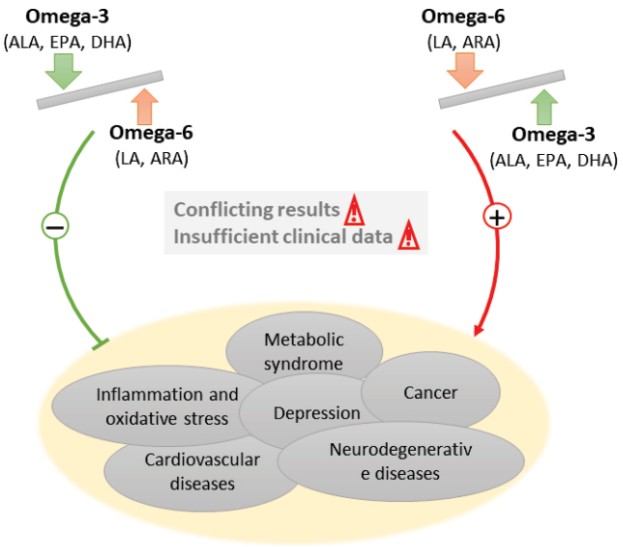

Fig 2: Implications of polyunsaturated fatty acids in different pathological conditions

Most of the experimental, epidemiological, and clinical studies have revealed the role of a balanced/imbalanced omega-6/omega-3 ratio in the disease prevention/manifestation. However, some controversies about omega-3 beneficial effects and lack of clinical data emphasize upon the need for further investigation. ALA, α-linolenic acid; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; LA, Linoleic acid; ARA, arachidonic acid. (-) indicates inhibition/protection while (+) indicates induction/risk related to various diseases.

cardiovascular diseases.[24] A meta-analysis comprising of 20 cross-sectional and seven case-control studies showed that higher levels of plasma/serum omega-3 PUFAs were related with a reduced MetS risk.[25] Owing to their anti-inflammatory and lipid-lowering properties, omega-3 PUFAs supplementation has been found to improve the individual features of MetS, thus conferring protection from cardiometabolic disorders.[26]

Several studies have shown that fish and fish oil-derived omega-3 PUFAs could decrease plasma lipid levels, insulin resistance, and blood pressure, remediating the effects of MetS.[27] The consumption of EPA and DHA reduced serum triglycerides in type 2 diabetes mellitus.[28] However, the longitudinal cohort study indicated an inverse relationship of the serum omega-6 PUFAs levels with the incidence of MetS.[29] Nevertheless, the studies based on meta-analyses of randomized controlled trials (RCTs) did not show any effectiveness of omega-3 and omega-6 PUFAs in the prevention or treatment of type 2 diabetes or insulin sensitivity, suggesting further clinical investigation in order to attain a conclusive evidence.[30,31]

Obesity is a multifactorial chronic disease caused by the accumulation of excessive/abnormal fat associated with dyslipidemia, insulin resistance, hypertension and MetS. Studies have shown that the fish oil supplementation leads to elevated plasma adiponectin and leptin levels with an improved plasma lipid profile in comparison with a sucrose-fed diet in insulin-resistant rats.[32] In addition, fish-based dietary supplementation of non-obese healthy Japanese volunteers showed higher serum omega-3 PUFAs and adiponectin levels[33], indicating the significance of the consumption of the diet rich in omega-3 fatty acids for the maintenance of body weight. Since few intervention trials have been conducted regarding omega-3 supplementation in obesity, there is limited suggestive evidence about the anti-obesity effects of omega-3 PUFAs, emphasizing upon the need for more clinical trials.[34,35]

Cardiovascular health

Cardiovascular diseases (CVDs) are considered to be the leading cause of worldwide mortality, with 32% of the 56 million deaths in 2015.[36] Globally, the individuals have been recommended to replace saturated fatty acids with polyunsaturated fatty acids in the diet for coronary heart disease risk reduction, owing to the cardioprotective effects of omega-3 fatty acids including lowering of blood pressure and cholesterol levels.[37] Omega-3 PUFAs such as EPA and DHA mainly contribute in preventing cardiac arrhythmias, decreasing platelets aggregation, reducing inflammation, lowering plasma triglycerides and reducing blood pressure.[38] They have also been found effective in enhancing the arterial endothelial function and reducing the expression of vascular adhesion molecules.[39] In addition, early RCTs showed a reduced risk of mortality from CVDs with a higher intake of fatty fish or omega-3 PUFAs dietary supplements.[40] The mechanisms of these PUFAs have been found to be similar to the pleiotropic effects of statins by improving endothelial functions and exerting antioxidant and anti-thrombotic effects.[41]

These results are further supported by animal studies, as rats fed with 12% fish oil (12% DHA, 18% EPA) exhibited significantly smaller infarct size as

compared to control group.[42] In addition, dietary supplementation of 12% fish oil in rats (13% DHA, 19% EPA) exerted cardioprotective effects against ischemia and reperfusion in isolated rat hearts.[43] Additionally, a significant reduction in myocardial infarct size was observed in rabbits supplemented with EPA (600 mg/kg/day)[44] and in pigs treated with DHA (45 mg)[45], as compared to their respective controls. In addition, protective effects of omega-3 PUFAs from fish have been of special interest in coronary artery disease (CAD). High intakes of EPA and DHA were found to be associated with decreased CAD mortality in ecologic population prospective cohort studies[46] and dietary intervention studies.[47] Interestingly, DHA was found to be consistently reduced in patients with coronary heart disease as compared with controls, further highlighting the cardioprotective functions of this fatty acid.[48] In middle-aged men from the ERA-JUMP study, high serum levels of LA and ARA were found to be linked with decreased concentrations of large very low density lipoprotein (VLDL) and increased levels of high density lipoprotein (HDL) particles, which have been found to be associated with increased risk for CAD.[49]

Though a large body of evidence has supported the beneficial effects of omega-3 fatty acids, some recent clinical trials have shown conflicting results on the association of PUFAs in patients with prior CAD, stroke or major vascular outcomes.[50] The randomized placebo-controlled trials including A Study of Cardiovascular Events in Diabetes (ASCEND)[51] and Vitamin D and Omega-3 Trial (VITAL) have revealed that the supplementation with omega-3 PUFAs (1 g/day) has no effects on major cardiovascular events.[52] Furthermore, the studies based on meta-analysis of large RCTs showed little or no association of omega-3 fatty acids with the risk of fatal and nonfatal coronary heart disease and major vascular events.[53,54] Further investigation is required to develop a better understanding of the effects of omega-3 PUFAs on various CVD outcomes as well as to identify the optimal dose and risk-benefit balance for each individual receiving the therapy.

Inflammation

Inflammation is a body defense mechanism against pathogens and infections attacking the host along with tissue repair and hemostasis restoration. It is a self-regulatory process that involves secretion of anti-inflammatory mediators and activation of regulatory cells with the inhibition of signaling cascades that are pro-inflammatory.[55,56] Fatty acids regulate inflammatory processes through different mechanisms involving membrane fluidity, surface/intracellular receptor binding, and cell signaling control, ultimately leading to the alterations in gene expression. Studies have shown that a high-fat diet alters the distribution of gut microbes and metabolic processes, activates inflammatory signaling pathways, resulting in an elevated number of inflammatory biomarkers such as TNF-α, IL-1 and IL-6.[57] The enrichment with omega-3 PUFAs has been shown to reduce the levels of ARA and hence the production of ARA-derived pro-inflammatory eicosanoids *e.g.,* leukotrienes, prostaglandins and thromboxanes.[55] It has also been identified previously that the anti-inflammatory actions of EPA and DHA are largely responsible for their therapeutic efficacy in inflammation-related conditions including rheumatoid arthritis, dyslipidemia, diabetes, obesity, atherosclerosis, plaque rupture, cardiovascular and neurodegenerative diseases.[58] Feeding fish oil results in the replacement of ARA by EPA in cell membranes, leading to the reduced expression of cyclooxygenases and lipoxygenases, thereby decreased activation of pro-inflammatory cascade.[59] Studies have clearly shown that the protective effects of omega-3 fatty acids against various pathological conditions are largely mediated by their shifts in gut microbial populations, individual sensitivity and anti-inflammatory properties.[57, 60] However, some clinical studies and meta-analyses have shown inconsistent findings regarding the effects of PUFAs on the inflammatory status caused by various pathological conditions.[61-63] Keeping in view these inconsistent findings, further investigation is needed to explore the mechanism of action of PUFAs as well as their therapeutic doses for the treatment of patients with different underlying conditions.

Oxidative Stress

Elevated oxidative stress is linked with increased risks of various inflammatory and heart diseases.[64] The intake of omega-3 PUFAs particularly EPA and DHA has been considered as an effective preventive

strategy for the possible rise in lipid peroxidation, cytotoxicity and antioxidant modulation.[65] Omega-3 PUFAs are sensitive to oxidative stress due to the presence of multiple double bonds in their polyene chain[66] and therefore also contribute to the development of various pathologies related to the production of excessive free radicals, especially reactive oxygen species.[67] Oxidative stress also leads to unsaturated lipid peroxidation which enhances the disbalanced redox homeostasis. An important example in this regard is, retinal lipofuscin, which is formed by the accumulation of pigments in epithelial cells of retina leading to an excessive oxidative stress and as a result an increased cellular toxicity.[66,67] Omega-3 PUFAs have also shown antioxidant effects not only in retinal lipofuscin but also in CAD and related pathologies.[68] There are some studies that have examined the baseline relationship between biomarkers of oxidative stress and omega-3 PUFAs and have also shown successful association of inflammation and depression with omega-3 PUFAs treatment.[69] In particular, DHA and EPA are known to exhibit antioxidant effects by reducing the production of hydroxyl and superoxide radicals. However, treatment doses of PUFAs and individual responses of patients to treatment lead to variability in results.[70]

Depression

Depression is one of the leading causes of mental disorders that results in productivity loss among individuals and increases the ratio of accidents and suicidal deaths. It also creates economy burden due to costly and long-term treatment of patients.[71] Omega-3 PUFAs play important roles in brain functions and mood disorders, as EPA and DHA have been found in low levels in the patients' blood samples. These PUFAs can be absorbed through neuronal cell membranes and affect mood swings, therefore, the consumption of fish oil and certain marine algae is highly recommended for patients with depression.[72] This has also been studied in postpartum depression, manic depression, schizophrenia, attention seeking personality disorders and obsessive-compulsive disorders. The anti-inflammatory effects of these fatty acids may also be useful in depression and improving memory.[73] Clinical trials with nonsteroidal and anti-inflammatory drugs have shown the beneficial effects of omega-3 PUFAs in managing depression in randomized placebo-controlled trials.[72,73] However, due to the limited research and contradictory conclusions about the role of PUFAs in depression, further research is needed to reveal the benefits and risks associated with PUFAs treatment for the control of depression.

Cancer

The alterations in lipid composition have been reported in various cancer cell lines.[1] Though the cancer patients show an impaired nutritional status, few studies have been performed to determine their fatty acid composition. A large body of evidence has revealed the importance of omega-3 PUFAs in the prevention of cancer, whereas, omega-6 PUFAs have been reported to promote cancer development.[74,75] Therefore, the ratio 2-4:1 of omega-6/omega-3 is considered ideal to decrease the risk of cancer.[76] Hence the diets containing disproportionately high omega-6/omega-3 PUFA ratios are supposed to contribute to the development of cancer.

Epidemiological studies have shown that the consumption of a diet rich in omega-3 PUFAs exerts protective effects in suppressing the progression of different types of cancers including prostate, colon, breast and kidney cancer.[1,77-80] Interestingly, reduced levels of plasma omega-3 PUFAs were found in patients with pancreatic cancer and non-small cell lung cancer.[81] Bladder cancer cells showed high levels of stearic acid (18:0) and oleic acid (18:1*n*-9), whereas a significant reduction in ARA was detected in bladder cancer tissue, indicating changes in lipid metabolism during human bladder tumorgenesis.[82] In addition, patients with multiple myeloma showed significant increase in plasma levels of omega-6 PUFAs and decreased levels of omega-3 PUFAs compared with healthy controls.[83] Furthermore, the roles of an FDA-approved fish oil emulsion (Omegaven®) have been appreciated in the last years, as parenteral nutrition for postoperative recovery and as adjuvant in reducing chemotherapy-related toxicity in different cancers.[84,85]

In contrast, however, some recent clinical studies (VITAL research group) and meta-analysis of RCTs (PUFAH group) have shown conflicting results regarding the role of these PUFAs in various cancer types, suggesting that the omega-3 PUFAs supplementation did not lower the risk or incidence

of cancer.[52,86] The variability in the results can be attributed to the omega-3 PUFAs dose, omega-6/omega-3 PUFA ratios as well the genetic variability among individuals and requires further investigation.

Neurodegenerative Disorders

LC-PUFAs, notably DHA and ARA comprise about 15-30% of the brain's dry weight where they play key roles in enhancing brain functions and development at various stages in life, from perinatal period, child- and adult-hood to aging. They mainly influence the architecture and functions of central nervous system, thereby regulating the blood-brain barrier functions, neurotransmission, and neuronal membrane fluidity. Studies have shown that low plasma DHA levels are associated with cognitive or behavioral impairments during early development or aging.[87] Interestingly, an inadequate intake of maternal omega-3 PUFAs leads to a poor child's neural development and vice versa.[88] Furthermore, the deficiencies of these PUFAs in adults result in serious deficits in cognitive functions, leading to the onset of various age-related neurodegenerative disorders.[89]

Alzheimer's disease (AD) is the most common form of dementia, causing more than 70% of dementia cases worldwide in individuals older than 65 years.[90] AD is characterized by multiple cognitive impairments, memory loss and altered behaviors, including delusion and paranoia.[91] The pathology and symptoms of AD are poorly understood. Previous studies have linked AD to the respective neuroprotective and pathogenic effects of omega-3 and omega-6 PUFAs. However, how the imbalance in the ratio omega-3/omega-6 affects different stages of AD pathology is currently not fully understood.

The accumulation and aggregation of A has been found to be a central event in the pathogenesis of AD.[92] DHA and EPA have been found to increase Aβ42 elimination, thereby enhancing the neurotrophin levels and reducing the pro-inflammatory cytokine production.[93]

Epidemiological studies have suggested the higher intake of omega-3 PUFAs to be linked with reduced risk of AD.[94] Innumerable prospective studies have shown that an increased intake of omega-3 or fish oil is inversely associated with dementia and AD risks.[95] The protective role of DHA is mainly due to its presence in large amounts in neuronal membrane phospholipids, where it is involved in the maintenance of nervous system functions.[96] Furthermore, altered fatty acid profiles and low DHA levels were reported in different regions of brain in AD patients.[87]

In 2006, the first placebo-controlled RCT (OmegAD Study) treated patients from mild to moderate AD with omega-3 PUFAs (1.7 g DHA + 0.6 g EPA). The study did not show any reduction in decline rate of the cognitive dysfunction except for a subgroup of patients (n=32) with very mild cognitive impairment.[97] Furthermore, the data obtained from a systematic meta-analysis did not reveal any beneficial effects of omega-3 PUFAs in the treatment of mild to moderate AD[98], instigating the need to conduct highly controlled RTCs with longer treatment durations and optimal dose selection for each individual.

On the other hand, elevated levels of omega-6 PUFAs, particularly ARA were observed with PET scan in AD patients compared to healthy controls.[99, 100] Furthermore, an ARA-enriched diet has been shown to increase brain sensitivity towards the amyloid oligomer toxicity in mice.[101]

Moreover, higher intake of omega-6 PUFAs causes a large production of the ARA derived pro-inflammatory cytokines (*i.e.* TNF-α, IL-1, and IFN-γ) which results in brain damage.[102] Hence, the balance in the ratio of omega-6/omega-3 plays a significant role in the onset of AD, as lower ratios have been shown to decrease the possibility of developing dementia especially in depression patients.[103] Together, it can be suggested that patients having characteristics of cognitive impairments and dementia can be improved with an increased intake of omega-3 PUFAs or a balanced omega-6/omega-3 PUFAs ratio in the early stages of the disease.

Another neurodegenerative condition includes Parkinson's disease (PD), which was described in 1817 by James Parkinson as a complex age-related neurological syndrome, with common features including dementia, tremor, rigidity and depression in the later stage of the disease.[1, 104] High intake of omega-3 PUFAs was found to be neuroprotective, in an animal model of Parkinsonism, against a neurotoxin-induced decrease in dopamine in the striatum.[105] Furthermore, DHA has been shown to

induce the recovery of the dopaminergic system after an extensive Parkinson's injury in mice, suggesting that the role of DHA in neuro-recovery can be potentially exploited after PD diagnosis.[106]

There are insufficient clinical trials studying the role of PUFAs in PD, however *in vitro* and *in vivo* studies have shown EPA as potential adjunctive therapy for PD. A recent clinical trial explored the functions of DHA in decreasing dyskinesia in PD (ClinicalTrials.gov; identifier: NCT01563913). Moreover, another study showed the correlation of DHA supplementation with a lower risk of PD-associated depression.[107] A six-months treatment with fish oil (800 mg/d DHA and 290 mg/d EPA) showed 50% reduction in the Hamilton Rating Scale for Depression score in DHA-treated patients, suggesting that DHA supplementation reduced depression symptoms.[108] Furthermore, a randomized double-blind placebo-controlled clinical trial on 60 patients supplemented with 1000 mg of omega-3 with vitamin E supplements for three months showed beneficial effects in improving clinical symptoms associated with PD.[109] However, a case-control study has reported the lack of association between omega-3 PUFAs and PD development risk.[110] Further large randomized controlled clinical trials need to be conducted with relatively longer treatment durations to explore the role of PUFAs in PD.

Huntington's disease is an inherited neurodegenerative disorder caused due to dominant polyglutamine expansion located close to the N-terminus of the Huntingtin protein. A pilot study on the advanced (stage III) Huntington's disease showed that the patients treated with ethyl-ester of EPA (ethyl-EPA) had a beneficial effect on the orofacial abnormalities associated with this disease.[111] Recently, in order to cope with the oxidative damage caused by lipid peroxidation in HD, the diet enriched with deuterium-reinforced PUFAs (D-PUFAs) was fed to a knock in mouse model of HD (Q140), which represents motor deficits and cognitive decline.[112] Interestingly, the mice showed significant reduction in F_2-isoprostanes in the striatum (80%), suggesting that D-PUFAs may represent a promising new strategy in improving the HD core deficits in humans.

Moreover, some clinical studies have also observed the promising efficacy of omega-3 PUFAs in the prevention or onset delay of other neurological disease such as multiple sclerosis, amyotrophic lateral sclerosis, and epilepsy.[113,114]

The neuroprotective effects of omega-3 PUFAs have shown potential as adjunctive therapies for neurodegenerative diseases. However, these compounds may also have the potential to worsen the condition and essential measures should be taken while considering their roles in neurodegenerative disorders and targeted therapeutic interventions.

Conclusion

A growing body of evidence from experimental and epidemiological studies invigorated the investigation of the effectiveness of omega-3 PUFAs supplementation in clinical trials. Most of these trials have suggested that omega-3 PUFAs contribute significantly to the prevention, treatment and/or management of various pathophysiological conditions and do not raise serious safety concerns. PUFAs have gained considerable significance for the identification of risk factors associated with a wide number of pathological conditions, thus stratifying the individuals based on their health and disease status. However, some research findings have also shown conflicting results regarding the beneficial properties of omega-3 PUFAs in different diseases including CVDs, diabetes, cancer, and neurodegenerative disorders. Several reasons may explain these controversies and emphasize upon the careful consideration of different treatment parameters, such as the natural sources containing different amounts of PUFAs, the chemical form and the quality of PUFAs formulations affecting their bioavailability, the omega-6/omega-3 ratio as well as the omega-3 index indicating the PUFAs enrichment in different organs. This may lead to variable effects in different clinical trials as well as in the studies based on meta-analyses of these trials. Therefore, there is an evident need to conduct highly controlled RCTs with larger sample sizes and longer duration of supplementation in order to assess the therapeutic potential of these PUFAs for different age groups, and also taking into consideration the ethnicity as well as individuals' genetic backgrounds.

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