

Omega-3 fatty acids: a comprehensive review of their role in health and disease

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ABSTRACT

Omega-3 fatty acids (ω -3 FAs) are essential fatty acids with diverse biological effects in human health and disease. Reduced cardiovascular morbidity and mortality is a well-established benefit of their intake. Dietary supplementation may also benefit patients with dyslipidaemia, atherosclerosis, hypertension, diabetes mellitus, metabolic syndrome, obesity, inflammatory diseases, neurological/ neuropsychiatric disorders and eye diseases. Consumption of ω -3 FAs during pregnancy reduces the risk of premature birth and improves intellectual development of the fetus. Fish, fish oils and some vegetable oils are rich sources of ω -3 FAs. According to the UK Scientific Advisory Committee on Nutrition guidelines (2004), a healthy adult should consume a minimum of two portions of fish a week to obtain the health benefit. This review outlines the health implications, dietary sources, deficiency states and recommended allowances of ω -3 FAs in relation to human nutrition.

Omega-3 fatty acids (ω -3 FAs) are essential fatty acids (EFAs) important in human nutrition. Their potential health benefits have been the focus of much research in the past two decades. The biological roles of these molecules were brought to the notice of the scientific community by the observation of low rates of coronary heart disease (CHD) among the populations of Japan and Greenland, where fish is an important component of the diet. Fish is a rich source of ω -3 FAs, and the inverse association between fish intake and the risk of mortality from coronary artery disease, observed in studies from the Netherlands,¹ Sweden² and the USA³ during the 1980s, has been proposed to be due to the beneficial effects of these essential biomolecules.

Many subsequent studies have shown the benefits of dietary consumption of ω -3 FAs in cardiovascular disease,^{4–11} dyslipidaemia,^{6 12 13} atherosclerosis,^{14–17} hypertension,^{18 19} diabetes mellitus,²⁰ metabolic syndrome,²¹ vascular reactivity,^{22 23} obesity,²⁴ inflammatory diseases,^{25–29} neurological/ neuropsychiatric disorders,^{30–32} renal disease,³³ osteoporosis,³⁴ eye diseases^{35–37} and pregnancy.^{38–40} With greater focus on chronic disease prevention globally, the role of ω -3 FAs in human health has become an area of interest for clinicians. This review is an attempt to outline their biological roles in relation to human health and disease.

EFAS

EFAs are polyunsaturated fatty acids that cannot be synthesised in the body and hence have to be supplied in the diet. Dietary EFAs are subclassified as ω -6 and ω -3 fatty acids, indicating the location of the carbon involved in the first double bond from

the omega end of their carbon chains.⁴¹ Linoleic acid (ω -6) and α -linolenic acid (ω -3) are the only EFAs known to be essential for complete nutrition of many species of animals including humans. These EFAs give rise to eicosanoic acids, from which are derived families of compounds known as eicosanoids which make up the prostaglandins, thromboxanes, leukotrienes and lipoxins. Figure 1 shows the sources, metabolic fate and metabolic products of EFAs.⁴² Box 1 shows the important biological roles of EFAs⁴² in the human body.

Since EFAs are unstable because of the presence of two or more double bonds in their structure, substantial loss occurs during food processing and hydrogenation of oils. On exposure to high temperatures and during hydrogenation, EFAs are converted into trans-fatty acids which may be harmful to the body. Figure 2 depicts the classification of fatty acids relevant to human metabolism.

In adults subsisting on an ordinary diet, EFA deficiency has not been reported. However, infants receiving formula diets low in fat and patients maintained for long periods on intravenous nutrition without supplemental EFAs can develop EFA deficiency. Deficiency can be prevented by a daily intake of EFAs amounting to 1–2% of the total energy requirement.⁴² Table 1 compares the manifestations and biochemical markers of EFA deficiency.

ω -3 FAS IN HEALTH

Studies of Paleolithic nutrition and that of the hunter-gatherers have shown that the ancient populations consumed much less saturated fat, roughly equal amounts of ω -6 and ω -3 FAs (ratio of 1–2:1) and much lower amounts of trans-fatty acids than the present-day Western populations.^{43 44} The current Western diet is very high in ω -6 FAs (the ratio of ω -6 FA to ω -3 FA is 20–30:1) because of decreased fish consumption and increased consumption of food items rich in ω -6 FAs.⁴⁴

Consumption of higher amounts of ω -6 FAs increases the plasma concentrations of eicosanoid metabolic products from arachidonic acid, specifically prostaglandins, thromboxanes, leukotrienes, hydroxy fatty acids and lipoxins. These bioactive products contribute to the formation of thrombi and atheromas in blood vessels, development of allergic and inflammatory disorders, and excessive cell proliferation.⁴⁴ ω -3 FAs on the other hand counteract these deleterious effects of ω -6 FAs by decreasing the production of thromboxane A₂ (a potent vasoconstrictor and platelet aggregator), prostaglandin E₂ metabolites and leukotriene B₄ (inducer of inflammation and leucocyte chemotaxis and adherence), and increasing concentrations of vasodilatory prostacyclins such as prostaglandin I₃.⁴⁴

Box 1: Important biological functions of essential fatty acids

- ▶ Cell membrane formation, integrity and functions
- ▶ Functioning of brain, retina, liver, kidney, adrenal glands and gonads
- ▶ Local hormone production
 - Prostaglandins, leukotrienes and thromboxanes
 - Regulation of blood pressure, viscosity of blood, vasoconstriction, immune and inflammatory responses

stroke in different populations may reflect the different patterns and types of fish consumed and the preparation methods.^{65 67} The ongoing SU.FOL.OM3 Study⁶⁸ may provide satisfactory evidence regarding the role of ω -3 FAs in the secondary prevention of ischaemic stroke.

A recent meta-analysis did not show significant benefits of ω -3 FAs in patients with peripheral arterial disease in terms of clinical outcomes such as ankle-brachial pressure index, systolic blood pressure, plasma viscosity, pain-free walking distance or maximal walking distance, with the exception of a reduction in blood viscosity.⁶⁹ Although another recent clinical trial showed marked improvement in endothelial function in subjects treated with ω -3 FAs,⁷⁰ routine use of these molecules for treating patients with peripheral arterial disease may not be justified until more evidence for their beneficial effect is available.

Dyslipidaemia

The major effect of ω -3 FAs on lipids is associated with their ability to reduce plasma triglyceride concentration.^{6 12 13 19} Both fasting and postprandial concentrations of triglycerides are reduced by ~24%.⁷¹ The ratio of triglycerides to HDL-cholesterol (the atherogenic index), an important atherogenic risk factor, has been found to be lower in people treated with ω -3 FAs.²⁰ Reduced very-low-density lipoprotein cholesterol was another beneficial effect.^{19 72} Although increases in plasma HDL-cholesterol concentrations were noticed in several studies,^{6 12 13 20 24 56} there were no significant changes in HDL-cholesterol concentrations in other studies.^{71 72}

One adverse lipid abnormality observed with administration of ω -3 FAs was a marginal increase in LDL-cholesterol in treatment groups.^{71 72} However, the LDL particle size was observed to be higher and the quantity of small dense LDL particles was observed to be less.^{49 57 71} This observation has important clinical implications, as larger LDL particle sizes are associated with less risk of atherosclerosis. A reduction in the highly atherogenic lipoprotein (a) fraction of plasma is another important beneficial effect of treatment with ω -3 FAs.¹²

Atherosclerosis

Beneficial effects of ω -3 FAs on atherosclerosis are mainly through their actions on plasma lipids. Effects such as blood pressure reduction,^{6 18 21} reduction of plasminogen activator inhibitor,^{12 20} and improvement in metabolic syndrome^{21 24 56} and endothelial function²¹⁻²³ may be the other potential antiatherogenic factors. As atherosclerosis is an inflammatory disease, ω -3 FAs may also offer protection through their anti-inflammatory effects. Serum and peripheral blood mononuclear cell concentrations of proinflammatory cytokines such as IL1 β , tumour necrosis factor α and IL6 were found to be lower in hypercholesterolaemic subjects treated with ω -3 FAs.⁷³ Dietary

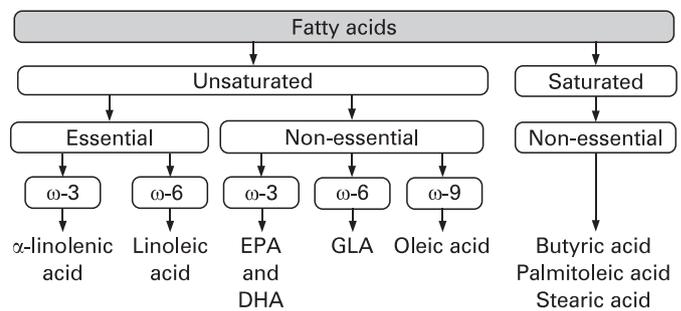


Figure 2 Classification of fatty acids relevant to human metabolism. EPA, eicosapentanoic acid; DHA, docosahexanoic acid; GLA, γ -linolenic acid.

intervention with oil-rich fish has been shown to reduce platelet-monocyte aggregation, a sensitive marker of platelet activation that contributes to the initiation and progression of atherothrombosis.⁷⁴ Through their anti-inflammatory effects, ω -3 FAs may prevent atheroma formation and also stabilise atherosclerotic plaques.

Many studies on the antiatherosclerotic effects of ω -3 FAs are secondary prevention trials on patients with CHD, and current evidence may justify their use in high-risk patients.¹⁴⁻¹⁷ The absolute difference in restenosis rates between the treated group and controls after coronary angioplasty was 13.9%, and a positive linear relationship was observed between the dose of ω -3 FAs and restenosis rates.¹⁵ Trials of the use of ω -3 FAs for secondary prevention of coronary atherosclerosis have shown greater benefits for patients with diabetes mellitus.¹⁷ Diabetic patients treated with ω -3 FAs showed significant improvements in the carotid intima-media thickness and the brachial-ankle pulse-wave velocity, indicating that they are useful for treating atherosclerosis in other vascular beds also.⁷⁵ ω -3 FA supplementation was also associated with favourable effects on the arterial elasticity of carotid vessels in older men with dyslipidaemia.⁷⁶

Hypertension

The blood pressure-lowering effect of ω -3 FAs is well established in both hypertensive^{18 19 77 78} and normotensive⁷⁷ subjects. ω -3 FAs reduce both systolic and diastolic blood pressure. People consuming ω -3 FAs on a regular basis have been found to be less likely to develop hypertension.⁶ Most studies investigating the effect of fish oils in reducing blood pressure used higher doses (median dose 3.7 g/day), and a reduction in systolic blood pressure of 2.1 mm Hg and diastolic blood pressure of 1.6 mm Hg has been observed.⁷⁸ Beneficial effects of ω -3 FAs on blood pressure reduction tended to be greater in older subjects (age >45 years) and hypertensive patients. The antihypertensive effects of lower doses are yet to be defined.

The International Study of Macro- and Micro-nutrients and Blood Pressure (INTERMAP), an international cross-sectional epidemiological study of 4680 men and women aged 40-59 years from 17 population-based samples in China, Japan, UK and USA, has shown an inverse relationship of total dietary ω -3 FAs to systolic and diastolic blood pressure.⁷⁷ Findings of the Atherosclerosis Risk in Communities (ARIC) Study indicated that an increase of 1 SD in dietary ω -3 FAs (calculated as percentage of energy intake) and balancing ω -3/ ω -6 FAs decreased the risk of a 6-year cognitive decline in verbal fluency in hypertensive patients, with an odds ratio (OR) of 0.79 and 0.81, respectively.⁷⁹ Although the reduction in blood pressure in treatment groups was modest, the observations from these

Table 1 Dietary sources of essential fatty acids and manifestations and biochemical markers of deficiency

Essential fatty acid	Dietary source	Deficiency	
		Manifestations	Biochemical markers
ω -3 FA	Walnuts, wheat germ oil, flaxseed oil, canola oil, fish oil, human milk, organ meats, seafood, fatty fish (albacore tuna, mackerel, salmon, sardines)	Reduced learning, impaired vision, abnormal electroretinogram, polydipsia	Decreased ω -3 Increased ω -6, ω -7 and ω -9
ω -6 FA	Corn oil, peanut oil, cottonseed oil, soybean oil, many plant oils	Growth retardation, skin lesions, reproductive failure, fatty liver, polydipsia	Decreased ω -6 Increased ω -9

studies may be important in designing treatment plans and population-based preventive strategies for hypertension.

Diabetes mellitus

The major benefit of ω -3 FAs in patients with type 2 diabetes mellitus is improvement in their highly atherogenic lipid profile. They may also reduce insulin resistance. Although some studies^{20 49 56 72} have not shown significant changes, others have shown improved insulin resistance in treatment groups.^{21 24} The Diabetes Autoimmunity Study in the Young (DAISY), conducted among children at increased risk of developing type 1 diabetes, showed that development of pancreatic islet-cell autoimmunity was significantly lower in those treated with ω -3 FAs.⁸⁰ The promising results of this study are now under further evaluation for designing prevention strategies of this major incurable disease.

Obesity

Obesity has become a major public health problem worldwide, and it contributes significantly to the high prevalence of lifestyle diseases such as diabetes mellitus, hypertension and cardiovascular disorders. Weight loss through dietary and lifestyle modifications reduces the risk of developing these diseases and forms the main strategy for the management of these patients. Incorporation of ω -3 FAs as a component of a weight-loss diet was associated with a greater reduction in fasting plasma concentrations of insulin, glucose and triglycerides in obese patients.²⁴ Such an intervention was also accompanied by a specific improvement in markers of oxidative stress in patients with obesity.⁸¹

Metabolic syndrome

Metabolic syndrome is an important cause of cardiovascular morbidity in the developed countries. Widespread endothelial dysfunction is a hallmark of this disease that makes the patients vulnerable to atherosclerosis and cardiovascular disorders. Weight-loss and dietary modifications are the cornerstones of

management of metabolic syndrome. Dietary supplementation of ω -3 FAs has been shown to improve all components of the disease.^{21 24 56} Endothelial function scores also improved in the treatment group.²¹ Thus ω -3 FAs may be recommended as an integral component of treatment of patients with metabolic syndrome.

Gastrointestinal disorders

Dietary supplementation of ω -3 FAs has been associated with an improvement in disease activity and weight gain in patients with active ulcerative colitis.²⁵ However, a recent meta-analysis has not shown evidence to support their routine use for maintenance of remission.⁸² Although administration of ω -3 FAs as enteric-coated capsules was shown to be safe and effective for maintenance of remission in patients with Crohn disease in a small study,²⁷ two recent large multi-centric randomised, double-blind, placebo-controlled studies did not show significant benefits of their use.⁸³

Even though regular ω -3 FA supplements may provide some benefits for people with cystic fibrosis with relatively few adverse effects, in the absence of sufficient data, routine supplementation cannot be recommended.⁸⁴ Similarly, in some cohort studies, dietary ω -3 FAs in the form of fish consumption has been shown to reduce colorectal cancer risk, but large-scale data are not available.⁸⁵

Rheumatological conditions

ω -3 FAs have been shown to be effective in the management of pain associated with several inflammatory joint disorders. Dietary supplements of fish oil can be used as a non-steroidal anti-inflammatory drug (NSAID)-sparing agent in patients with rheumatoid arthritis.^{26 29} A recent meta-analysis of 17 randomised, controlled trials assessing the pain-relieving effects of ω -3 FAs in patients with rheumatoid arthritis or joint pain secondary to inflammatory bowel disease and dysmenorrhoea showed significant improvements in patient-reported joint pain intensity, duration of morning stiffness, number of painful and/or tender joints, and NSAID consumption at 3–4 months.⁸⁶ The mechanism of the anti-inflammatory and analgesic properties of ω -3 FAs may be their ability to inhibit cytokine production and inflammatory mediators at cellular and tissue concentrations.

Neurological/neuropsychiatric disease

Many neurological and neuropsychiatric disorders do not have curative treatments. Potential benefits of ω -3 FAs in some of these disorders have been investigated recently. Docosahexanoic acid (DHA), an ω -3 FA found abundantly in normal human brain, has been shown to be decreased in the brain and plasma of patients with dementia.⁸² Subjects with high plasma DHA concentrations (those with a mean fish intake of 3.0 servings a

Table 2 Dietary recommendations for ω -3 FAs by various scientific bodies

Professional body (year)	Recommendation
UK Scientific Advisory Committee on Nutrition (2004)	Minimum of 2 portions of fish/week (one oily) that is equivalent to 450 mg EPA + DHA
World Health Organization (2003)	Up to two fish meals/week (400–1000 mg EPA+DHA)
US National Academies of Science, Institute of Medicine (2002)	1.4 g α -linolenic acid/day (~140 mg EPA+DHA)
American Heart Association (2002)	~1g/day ω -3 FA for secondary prevention of CHD

CHD, coronary heart disease; DHA, docosahexanoic acid; EPA, eicosapentanoic acid.

Review

week) had a 47% reduction in the risk of developing all-cause dementia in a cohort from the Framingham Heart Study.³² Improved motor function in patients with Huntington disease has been reported with ω -3 FA treatment.³¹

An association between depression and low dietary intake of ω -3 FAs has been observed in several studies. A recent meta-analysis showed that treatment with ω -3 FAs can improve patients with clearly defined depression and bipolar disorders.⁸⁷ Prevention of excessive aggression at times of high mental stress in young adults³⁰ and improvement in behaviour, reading and spelling performance of children with developmental coordination disorder⁸⁸ are the other reported beneficial effects of ω -3 FAs that may evoke enthusiasm for future research.

Eye diseases

Meta-analysis of pooled data from nine studies showed that high dietary intake of ω -3 FAs was associated with 38% reduction in the risk of late age-related macular degeneration (AMD).³⁵ Fish intake at least twice a week was associated with reduced risk of both early AMD (pooled OR 0.76) and late AMD (pooled OR 0.67). Treatment with ω -3 FAs has also been associated with improvement in some of the clinical outcomes in patients with retinitis pigmentosa.³⁶ The incidence of dry eye syndrome was less common among women who consumed higher amounts of ω -3 FAs.³⁷

Other medical conditions

Supplementation with ω -3 FAs has been shown to benefit children and adults with IgA nephropathy by reducing proteinuria in a dose-dependent manner.³³ Alterations in renal haemodynamics and inflammation through reduced cytokine production is the probable mechanism of protection. A ω -3 FA-rich diet has been shown to reduce cytokine concentrations and inflammatory mediators in patients with chronic obstructive airway disease, with significant improvements in their clinical outcomes.²⁸ A high ratio of dietary ω -6/ ω -3 FAs has been shown to be independently associated with low bone mineral density.³⁴ The results of this study suggest that supplementation with ω -3 FAs may improve skeletal integrity in old age and may reduce the risk of osteoporosis and fractures.

Main messages

- ▶ Omega-3 fatty acids (ω -3 FAs) are important essential fatty acids that should be included in the human diet for maintenance of normal health and nutrition.
- ▶ ω -3 FAs reduce cardiovascular morbidity and mortality by reducing arrhythmia risk, decreasing blood pressure, improving the atherogenic lipid profile and reducing platelet aggregation.
- ▶ ω -3 FAs have proven beneficial effects in patients with metabolic syndrome, obesity, type 2 diabetes mellitus, depression, degenerative disorders of the eyes and pain associated with arthritis.
- ▶ Maternal intake of ω -3 FAs reduces risk of premature birth and enhances intellectual development of the fetus and infant.
- ▶ About two portions of fish a week or an equivalent of 1 g ω -3 FAs a day from other dietary sources amounting to 0.6–1.2% of total energy requirement per day is recommended for a healthy adult.

ω -3 FAS AND PREGNANCY OUTCOMES

Maternal intake of ω -3 FAs has been shown to reduce the chance of premature birth.³⁸ Maternal supplementation during pregnancy and lactation has also been shown to improve the mental development of the child.³⁹ ω -3 FAs are important in development of the nervous system, and a poor supply of these essential nutrients during fetal and immediate neonatal life may adversely affect intelligence.

The World Association of Perinatal Medicine Dietary Guidelines Working Group recommends that the fetus and neonate should receive ω -3 FAs in amounts sufficient to support optimal visual and cognitive development.³⁸ Pregnant and lactating women should aim to achieve an average daily intake of at least 200 mg DHA. To achieve this goal, women of child-bearing age should aim to consume one to two portions of sea fish a week. Intake of the DHA precursor, α -linolenic acid, was found to be far less effective with regard to DHA deposition in fetal brain than preformed DHA from oily fish.⁴⁰ Breast feeding supplies adequate amounts of preformed ω -3 FAs to healthy neonates, and when breast feeding is not possible, use of an infant formula providing DHA at levels of 0.2–0.5 weight percent of total fat is recommended.³⁸

DIETARY RECOMMENDATIONS

Table 2 shows the dietary recommendations for ω -3 FAs⁸⁹ given by various scientific bodies. The ω -3 FA content of the diet to achieve nutritional adequacy, defined as the amount necessary to prevent deficiency symptoms, is 0.6–1.2% of energy for α -linolenic acid, and up to 10% of this can be provided by eicosapentanoic acid (EPA) or DHA.

The *Dietary Guidelines for Americans 2005* report states, "Evidence suggests consuming approximately two servings of fish per week (approximately 227 g; 8 ounces total) may reduce the risk of mortality from CHD and that consuming EPA and DHA may reduce the risk of mortality from cardiovascular diseases in people who have already experienced a cardiac event".⁹⁰

Although the recommendations from various professional bodies are for consumption of fish, vegetarians who do not consume fish may use fish oil capsules⁸⁹ or certain vegetable oils with significant ω -3 FA content. The following vegetable seed oils are listed in decreasing order of their ω -3 FA content: linseed oil, flaxseed oil, pumpkin seed oil, canola oil, soybean oil, safflower oil and sunflower oil.

ADVERSE EFFECTS

Mild dyspepsia and belching are the main adverse effects reported with the use of fish oil in the diet. Environmental toxins such as mercury and polychlorinated biphenyls may contaminate marine products such as fish and may result in

Current research questions

- ▶ The therapeutic role of omega-3 fatty acids (ω -3 FAs) in patients with inflammatory diseases, neurodegenerative disorders, peripheral vascular diseases, osteoporosis and renal diseases requires further study.
- ▶ The potential benefits of ω -3 FAs for improving intellectual performance of mentally subnormal children need more clarification.
- ▶ More studies are required to determine the role of ω -3 FAs in the prevention of type 1 diabetes mellitus among children with increased risk of this disease.

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potential harm to humans. Local advisories may be useful for guidance on the safety of fish caught from lakes, rivers and coastal areas.⁸⁹

CONCLUSIONS

Dietary supplementation of ω -3 FAs has emerged as an important option for reducing the risk of cardiovascular morbidity and mortality over the past two decades. More recent studies have shown their beneficial effects in other lifestyle diseases such as metabolic syndrome, dyslipidaemia, atherosclerosis and diabetes mellitus. The anti-inflammatory effects of ω -3 FAs can be utilised in the management of some inflammatory joint diseases. They may also be effective in the treatment of certain degenerative neurological and eye diseases, IgA nephropathy, depression and learning disorders. Supplementation during pregnancy reduces the risk of premature birth and improves the intellectual development of the fetus. More studies are required to identify the potential benefits of ω -3 FAs in the treatment of renal diseases, dementia, inflammatory bowel disease, obesity, cancer and osteoporosis. At least two servings of fish a week or 1 g ω -3 FAs a day should be taken by an adult to obtain the health benefits of this essential nutrient.

SELF-ASSESSMENT QUESTIONS (TRUE (T)/FALSE (F); ANSWERS AFTER THE REFERENCES)

1. Butyric acid, palmitoleic acid and oleic acid are essential fatty acids.
2. Cardiovascular protection offered by ω -3 fatty acids is through reduced risk of arrhythmias, decreased platelet aggregation and improved lipid profile.
3. Lipoxins and prostaglandin D₂ are derived from ω -3 fatty acids.
4. Eicosapentanoic acid and docosahexanoic acid have important roles in brain, retina, liver, kidney, adrenal glands and gonads.
5. The recommended daily dose of ω -3 fatty acids is 1 g/day.

Competing interests: None.

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Answers

(1) F (α -linolenic acid and linoleic acid are essential fatty acids); (2) T; (3) F (they are derived from ω -6 fatty acids); (4) T; (5) T



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