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AFRICAN JOURNAL OF FOOD, AGRICULTURE, NUTRITION AND DEVELOPMENT
SCHOLARLY, PEER REVIEWED
Volume 24 No. 11
November 2024
PUBLISHED BY AFRICAN SCHOLARLY SCIENCE COMMUNICATIONS TRUST
ISSN 1684 5374

Guest Editorial

THE ROSY AND NOT TOO ROSY EFFECTS OF OMEGA-3 FATTY ACIDS' INTAKE

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https://doi.org/10.18697/ajfand.136.ED149

The omega-3 fatty acids are some of the most talked about nutrients in human nutrition, currently. While we desire to experience optimal well-being from the intake of the recommended levels of the omega 3 fatty acids, their excessive consumption can result in some undesirable effects, just as there are also unpleasant effects from the intake of low amounts in diets, such as dry scaly skin. However, their normal levels in diets pose no risks on human nutrition and metabolism. Some information regarding these health-acclaimed nutrients is as follows:

What are Omega-3 Fatty Acids?

Foods are made up of lipids, among which are fatty acids. The main dietary fatty acids (FA) include saturated fatty acids (SAFA), monounsaturated fatty acids (MUFA) and the polyunsaturated fatty acids (PUFA). Among the PUFA, the omega-3 and omega-6 fatty acids are of interest in this article, though the discussion will focus mainly on the omega-3 FA, but with occasional mention of the roles of the omega-6 FA in human health. Linoleic acid, linolenic acid, alpha linolenic acid (ALA), arachidonic acid (AA), eicosapentaenoic acid (EPA), decosapentaenoic acid (DPA) and docosahexaenoic acid (DHA) are long chain PUFA, with the latter 3 often being referred to as the marine omega-3 FA. ALA is the most common plant-based and diet-derived omega-3 FA and also the main omega-3 FA in vegan diets. Gamma linoleic acid (GLA), linoleic acid (LA), and conjugated linoleic acid (CLA) are omega-6 FA.

Sources of the Omega-3 FA

Fish muscle, fish oils, nuts (especially walnuts), flaxseed and flaxseed oil, and leafy vegetables are good sources of omega-3 FA, with the type in plant foods being ALA [1]. Small amounts of ALA are found in beef from grass-fed ruminants. EPA, DHA and DPA are found naturally in krill, fish and fish oils, such that they are referred to as the marine omega-3 FA. Edible oils from sunflower seed, peanut, maize grain and palm nuts are excellent sources of the omega-6 FA, but they also contain small amounts of ALA. Although ALA is convertible to EPA, the conversion process is inefficient [2]. Algae and seaweed are excellent sources of omega-3 FA as ALA [3]. The amount of EPA and DHA in seafood and in supplements varies, depending for the latter, on the manufacturing process [4]. Different fish species contain varying amounts of the omega-3 fatty acids, with anchovies, salmon, sardines containing > 1,200 mg/100 g of cooked edible portion, while trout and swordfish contain approximately 400-500 mg/100 g of edible portion; the common aquaculture fishes of the tropics such as tilapia and catfish, sea fishes such as the groupers, Mahi Mahi, cod, halibut and haddock, contain less than 250 mg/100 g of cooked edible portion [1]. The low omega-3 FA content in aquaculture-produced fish is due to the inclusion of a high proportion of grain in fish feeds. Consuming less than the 100 g of edible portion of these tropical fish

https://doi.org/10.18697/ajfand.136.ED149

or no fish at all, may require that one seeks-supplementation, though mixed diets may just supply the required amounts of the omega-3 FA. Breast milk contains significant amounts of DHA [5], and is therefore a crucial source of the nutrient for babies. Commercially-prepared and fried fish such as that from restaurants and fast food establishments, should not be relied upon as the main source of the omega-3 FA, as they tend to be relatively lower in them and high in trans-fatty acids due to the high temperature of frying, which destroys the FA and alters their profiles [6], which may affect their bioavailability.

Benefits of Consumption of Omega-3 FA

Unfortunately, the typical modern diet for most societies, often contains more omega-6 than omega-3 FA. This is due to the common use of high omega-6 FA vegetable oils such as sunflower, maize and palm for cooking and baking, resulting in adverse changes in the omega-3 to omega-6 FA ratio. Low omega-3 diets may also adversely upset the ratio of the two FA. As the average human diet therefore provides adequate omega-6 FA, supplementation is not generally necessary for this class of FA. As both omega-3 and 6 FA play important roles in human health, it is important to keep the two balanced. Health experts and authorities recommend the ratio of omega-6 to omega-3 FA in a healthy diet should be 4:1 [7], though a recent study indicates a lower ratio is healthier and more protective against disease [8]. Advice to increase the ratio of the two FA should target an increase in the dietary intake of the omega-3 FA-from fish and other seafood, rather than lowering the intake of the omega-6 FA [9]. It has been shown that the ratio of 20:1 (omega-6: omega-3) is common in American diets [10], with the indication that the ratio is similar or higher in most other parts of the world [11] in studies of red blood cell omega-3 index (O3I). The resulting imbalance of omega-6 to omega-3 FA has been suggested to contribute to a higher risk of developing various health problems, such as heart disease [12], cancer [13], asthma [14], arthritis [15] and depression [16]. But, specifically, the higher ratio favours atherosclerotic plaque inflammation [17], which is a trigger of high-risk cardiovascular disease (CVD) events [18], and also leads to poor brain development and function [19]. Though regarded generally as beneficial in CVD amelioration, there is controversial evidence regarding the effects of omega-6 PUFA on CVD risk. Despite the beneficial impact of omega-6 PUFA supplementation on CVD outcomes being supported by some studies, other studies report conflicting results [20, 21]. One plausible mechanism that may explain the relationship between omega-6 PUFA and CVD is the increased production of 2-series prostaglandins and 4-series leukotrienes due to the high content of omega-6 PUFA in the diet, exerting pro-inflammatory effects and thus potentiating CVD risk [20, 21]. Highly unsaturated FA such as AA appear to be linked to an increase in low-density lipoprotein cholesterol (LDL-C) and very-low density lipoprotein (VLDL) susceptibility to oxidation, thus enhancing their atherogenic effect [20]. Also, some studies found no association between omega-6 PUFA intake and CVD risk. In the Sydney Diet Heart Study, a randomized control trial (RCT) of 458 participants aged 30–59 years with a recent coronary event, the replacement of SAFA with LA (an omega-6 FA) significantly increased all-cause mortality [22]. Also, a meta-analysis of 32 observational studies and 27 RCTs reported no correlation between omega-6 PUFA supplementation and coronary heart disease (CHD) [23].

Studies in pre-term and full-term infants suggest that getting enough omega-3 FA in the diet of the mother is essential for optimal visual development (eye and optic nerve development). Several studies have also shown that animals that do not get enough DHA in their diets, suffer visual impairment and degradation of the retina [24, 25], though one 2-year long, controlled study, recently showed this may be beneficial only in the early stages of loss of retinal integrity and disease onset [26]. Human studies have also shown that low levels of DHA and EPA are found in diabetic retinopathy, age-related macular degeneration (ARMD), dry eye disease (DED) and retinopathy of prematurity [25, 27], thus pointing to the important role that adequate levels of DHA and EPA play in retinal health and prevention of ocular dystrophies. Thus, chronic inflammation may play a role in the development of many common, degenerative and potentially devastating eye conditions, but specifically, the omega-3 FA seem to play a key role in the body's ability to regulate and balance inflammation. Over the 12 years that participants were followed in the landmark AREDS study (Age-Related Eye Disease Study), conducted by the US National Eye Institute, those that reported the highest intake of omega-3 FA in their diets, were 30% less likely to develop central geographic atrophy or wet ARMD [28].

It seems that omega-3 intake by an expectant mother is essential for brain and eye (neurological and visual) development of the foetus [19]. As omega-3 FA are significant components of breast milk, they may be necessary for infant nutrition and healthy development [29] as research has established that the addition of EPA and DHA to the diet of pregnant women, has a positive effect on visual and cognitive development of the baby [30]. However, Guillot *et al.* [31], showed that maternal DHA supplementation did not improve neurodevelopmental outcomes at 18 to 22 months' gestational age in breastfed, preterm neonates, though subgroup analyses in the same study suggested a potential benefit for language acquisition in preterm neonates born before 27 weeks' gestational age. Strømmen *et al.* [32], also found that enhanced nutrient supply to very low birth weight infants (<1,500 g birth weight), resulted in improved white matter maturation and head growth, thus implying some benefits of the omega-3 FA to the neonate.

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Some Not too Rosy Effects of Omega-3 FA intake as Supplements

High doses of the omega-3 FA >2,000 mg, but less than 4,000 mg/day, are generally regarded to be safe and are well tolerated, though there are reported adverse effects of their consumption as supplements [33, 34, 35]. A recent, systematic review of RCTs published between 1987 and 2023 concluded that the adverse effects of omega-3 PUFA containing EPA or DHA, or both, compared with controls (a placebo or a standard treatment), had significantly higher odds of occurrence of diarrhoea, dysgeusia, and bleeding tendency, but lower rates of back pain [35]. The most common and significant side effects of excessive supplement intake are gastrointestinal (e.g., nausea and bloating), dermatological (skin itching), and haematological (anticoagulatory effects) [33]. Other reported side effects of high dose consumption of the omega-3 FA in clinical trials, included increased bleeding risk [36], increased LDL-C production (though it increased LDL density) [37], and the inability to control blood sugar levels [38], meaning that there would be no benefit of omega-3 FA supplementation for diabetic patients. Other risks associated with excessive intake of supplemental omega-3 PUFA include altered platelet function and the potential for lipid peroxidation. Long-chain, highly unsaturated fatty acids such as EPA and DHA, are at high risk of peroxidation. Membrane phospholipid fatty acids can be vulnerable to peroxidation, resulting in free radical formation, which can be detrimental to proteins and DNA integrity [33]. However, in a study (though short), on young horses fed 60 mg/Kg of body weight daily for 60 days, omega-3 FA supplements did not negatively affect Vitamin E status or promote lipid peroxidation [39]. Nonetheless, systematic reviews that examined the safety profile of omega-3 FA, when doses of up to 4,000 mg/day were consumed, concluded that supplementation is well tolerated and that associated adverse events were of no clinical significance [40]. All in all, potential risks of omega-3 FA intake, should be assessed versus the potential benefits, with the adverse effects likely to be dose-dependent. Also, most side effects are apparent only with the intake of supplements, as the amounts of the omega-3 FA in diets are normally low, with amounts varying depending on the nature of the food and manner of processing. To avoid undesirable side effects, consumers should eat as much of the plant sources of omega-3 FA, as any adverse side effects from their consumption are minimal. The time at high temperature processing of food should be kept short in order to maximize dietary omega-3 retention and therefore their intake.

Conclusion and Recommendations for Development

Omega-3 FA include EPA, DHA and DPA, which are commonly referred to as the marine omega-3 FA, and, ALA being the plant-based type. Although ALA is convertible to EPA, the metabolic process is inefficient. Wild fish, fish oils, krill, microalgae and algal oils are the best sources of the omega-3 FA, with walnuts, flax seeds and flax seed oil being good

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plant sources of the FA, but as ALA. To improve health outcomes, health authorities recommend the intake of 1,000-2,000 mg/day of supplements as safe, though amounts of up to 4,000 mg/day can be tolerated.

Most adverse effects of the excessive intake of omega-3 FA are apparent only with the intake of supplements as amounts of the omega-3 FA in diets are normally low, with amounts varying depending on the nature of food and manner of processing. The significant and adverse effects include gastrointestinal (nausea and bloating), dermatological (skin itching), and haematological (anticoagulatory). Other uncommon adverse effects include bleeding risk, increased LDL-C production, the inability to control blood sugar levels and altered platelet function.

To minimize and avoid undesirable side effects, consumers should eat mainly plant sources of omega-3 FA. To reduce the generation of trans fatty acids from high temperature thermal fish processing and retain as much of the omega-3 FA, broiling, baking or grilling instead of frying are recommended. For individuals who do not eat fish, EPA, DHA and DPA, are manufactured commercially from microalgae and algal oil for their use. Tso improve the blood serum omega-3 index to ≥8%, the consistent and habitual intake of 1,000-1,500 mg/day for at least 12 weeks is recommended.

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