What health professionals should know about omega-3 fatty acid supplements

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Abstract

Omega-3 (n-3) fatty acids are essential to maintain satisfactory human health and need to be consumed in the diet. Western diets are often deficient in n-3 fatty acids because of an insufficient intake of cold water oily fish. The main n-3 fatty acids in fatty fish are eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). To date, no formally accepted dietary reference intakes for EPA and DHA exist, while international intake recommendations differ widely. Supplementation is an easy and convenient way of increasing dietary n-3 fatty acid intake, but very little information is available to health professionals when advising consumers on choosing a supplement to suit their lifestyle. Reliable nutrition information on product labels is vital since misleading information may lead to erroneous dosages with concomitant adverse effects. Since no formal regulatory structure for dietary supplements currently exists in South Africa, consumers depend on self-regulation within the industry for assurance of product quality, consistency, potency and purity of n-3 fatty acid supplements. Therefore, the aim of this article is to equip health professionals with proper knowledge with special reference to the bioavailability of fish oil supplements, reliability of labelling information, dietary intake recommendations, potential adverse effects and some general advice when purchasing n-3 fatty acid supplements.

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Introduction

Omega-3 (n-3) polyunsaturated fatty acids are a congregate of fatty acids that are essential in maintaining satisfactory human health. α-linolenic acid (ALA) is a plant-derived n-3 fatty acid, and serves as the parent fatty acid of the n-3 series. However, ALA cannot be produced in the human body and needs to be consumed in the diet. Through a series of steps, ALA is metabolised into eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Food sources of ALA include flaxseed (linseed) and the oils of walnut, rapeseed (canola) and soya. However, the conversion rates of plant-derived ALA to EPA are approximately 8-20% in humans, but the conversion from ALA to DHA is only 0.5-9%.[1] In contrast to plant-derived n-3 fatty acids, marine n-3 fatty acids contain preformed EPA and DHA which can be consumed directly from cold water oily fish, such as sardines, anchovies, Chinook salmon, Atlantic salmon, herring, trout and oysters.[2] The importance of marine-derived EPA and DHA has been comprehensively studied, but the role of the plant-derived counterpart ALA is uncertain, despite the fact that ALA is the principal n-3 fatty acid in the Western diet.[1] In general, EPA interferes with the arachidonic acid cascade,[3] demonstrating anti-inflammatory and anti-aggregatory characteristics, while DHA is essential for neurological development.

Marine-derived n-3 fatty acids have been linked to a number of beneficial effects in various disease and inflammatory related conditions. The role of chronic low-grade inflammation in the development and progression of chronic diseases,[4] including cardiovascular disease, type 2 diabetes, cancer, rheumatoid arthritis and Alzheimer's disease[5] is becoming increasingly important. The potent anti-inflammatory properties of n-3 fatty acids have been shown to play a preventative role in the development of these conditions. Other conditions with inflammatory components in which n-3 fatty acids might be of benefit include obesity, Crohn's disease, ulcerative colitis, type 1 diabetes, asthma, psoriasis, multiple sclerosis, cystic fibrosis and chronic obstructive pulmonary disease.[3] The protective effects of n-3 fatty acids against coronary heart disease[6] and their significance in neural and visual development[7] are well documented. Researchers are becoming more interested in the role of n-3 fatty acids in the prevention and treatment of psychiatric-related conditions, such as depression and attention deficit hyperactivity disorder.[8]

As it is not always possible to consume adequate amounts of n-3 fatty acids through the diet, interest in n-3 fatty acid supplements has soared. Certain groups of people are prone to n-3 fatty acid deficiencies so supplementation might be an option through which to increase their n-3 intake. Such risk groups include the geriatric population, pregnant women, individuals with compromised

nutritional status, and those with a limited variety in food selection which prevents them from achieving nutrient adequacy. However, information pertaining to dietary intake recommendations, the bioavailability of n-3 fatty acid supplements, labelling information and potential adverse effects is limited, and health professionals may not be able to advise consumers with sufficient information. These aspects are addressed.

Dietary intake recommendations

Dietary recommendations and advice for the intake of n-3 fatty acids have progressed notably over the past five years. However, no formal dietary reference intakes currently exist for EPA and DHA. Because of the wide range of reputed health benefits associated with EPA and DHA, a number of international organisations and agencies have proposed recommendations for EPA and DHA, as well as daily fish intake for health promotion and disease prevention. A summary of international recommendations on the dietary intake of fish and fish oil is listed in Table I.

Table I: Recommendations for omega-3 fatty acid intake in adults according to different bodies

Group	Recommendation
American Heart Association[9]	*Primary CHD prevention:* 500 mg/day EPA plus DHA or two portions fatty fish/week *Secondary CHD prevention:* 1 g/day EPA plus DHA
American Dietetic Association and Dietitians of Canada[10]	500 mg/day EPA plus DHA
Eurodiet[11]	200 mg/day EPA plus DHA
Fourth Joint Task Force of the European Society of Cardiology[12]	Two portions fatty fish/week *Secondary CHD prevention:* 1 g/day EPA plus DHA
United Kingdom Scientific Advisory Committee on Nutrition[6]	At least two servings/week, of which one should be oily and provide 450 mg/day EPA plus DHA
International Society for the Study of Fatty Acids and Lipids[13]	500 mg/day EPA plus DHA
Perinatal Lipid Intake Working Group[14]	At least 200 mg/day DHA during pregnancy and lactation
World Association of Perinatal Medicine, Early Nutrition Academy and Child Health Foundation (Pregnancy and Lactation)[15]	200-300 mg/day DHA

CHD: coronary heart disease, DHA: docosahexaenoic acid, EPA: eicosapentaenoic acid

The ideal is that these dietary intake recommendations for n-3 fatty acids should be achieved by consuming oily fish, as well as plant-derived n-3 fatty acid sources on a regular basis. For the consumer, meeting these dietary recommendations might be difficult to achieve, especially in vulnerable population groups, where a supplement might be helpful to increase their dietary intake of n-3 fatty acids. In order to reach a recommended intake of 500 mg/day[13] to 600 mg/day[16] EPA and DHA intake by using supplements, an intake of approximately 2 000 mg fish oil with a 180 mg EPA:120 mg DHA content ratio[17] would be required. To consume these amounts of EPA plus DHA through diet or non-supplementation, approximately 50 g/day of bluefin tuna, or 60 g/day of pilchards, or 52 g/day of salmon[2] should be consumed. These amounts will vary according to the geographic origin and harvest season of the fish. In addition, the preparation method of the fish prior to consumption influences levels of EPA and DHA. Regular consumption of quality supplements would be a more convenient method of supplying n-3 fatty acids in adequate amounts to consumers.

Bioavailability of omega-3 fish oil supplements

The bioavailability of dietary supplements refers to the proportion of a substance that the human gastrointestinal tract is able to absorb and assemble for use or storage.[18] In nature, virtually all fats and oils comprise triglycerides (TGs). The n-3 fatty acids present in fish are almost exclusively TGs. However, not all n-3 fatty acid formulations on the South African market are encapsulated as TGs, but may be processed to ethyl esters (EEs) or re-esterified TGs (rTGs)[19] by manufacturers.

Structure of the fatty acid

The bioavailability of EPA and DHA in TG, EE or rTG forms varies, and may be a concern for the South African consumer as South African fish oil supplement labels do not specify the form of n-3 fatty acids present. In the USA, the majority of n-3 fatty acid preparations are available as either EEs or rTGs.[20] The EEs are the esterified products of fatty acids and ethanol. This chemical process is known as trans-esterification and involves the removal of the glycerol backbone of the TGs by substituting them with ethanol. By using fractional distillation, which removes short-chain and saturated fatty acids, it is now possible for manufacturers of these supplements to allow for selective concentration of EPA and DHA to levels in excess of those found in natural fish oils. Esterification is also applied to deodorise the fish oil. These preparations are typically marketed as fish oil concentrates. Through the process of glycerolysis, it is possible to convert EEs back to TGs. This process removes the ethanol molecule and re-esterifies the EPA and DHA fatty acids back to a glycerol backbone, resulting in the formation of rTGs.[21]

Because of the absence of a glycerol backbone of EEs, their digestion is altered. Pancreatic lipase is the enzyme that hydrolyses the fatty acids from the ethanol backbone in the small intestine. However, the fatty acid ethanol bond of EEs is much more resistant to hydrolysis by pancreatic lipase, when compared to the hydrolysis of TGs in the natural form, and may reduce the bioavailability of EEs. Consequently, the digestion and absorption of EEs is significantly lower compared to TGs and phospholipids (PLs). EEs are also thought to be highly dependent on the fat content of a meal. Higher fat meals would stimulate pancreatic enzyme activity overall, and thereby enhance absorption.[22]

More recently, Dyerberg et al[20] conducted a two-week clinical trial on 72 healthy individuals divided into six groups. N-3 fatty acid preparations containing 3.3 g EPA and DHA per day in EE, free fatty acid, or rTG form, were administered to three of the groups. The remaining three groups received cod liver oil, or fish body oil or a placebo. Increases in the absolute values of EPA and DHA were measured in fasting-serum TGs, cholesterol esters and PLs. The

rTGs demonstrated maximum bioavailability (124%) of EPA and DHA, when compared to the group consuming natural fish oil, while the bioavailability of EE was less (73%). No significant difference between the bioavailability of free fatty acids (91%) and natural TGs was observed.

In another randomised clinical trial over a six-month period, 150 healthy individuals received moderate doses of EPA and DHA (1 680 mg/day), administered either as rTGs or as EEs. A placebo group receiving corn oil was also included. The n-3 index (EPA plus DHA in red blood cell membranes, expressed as a percentage of total fatty acids) was determined at baseline, after three, and six, months of treatment. After three months, it was reported that rTG levels resulted in a significantly increased n-3 index (186% increase from the baseline). In addition, this resulted in a more rapid incorporation of EPA and DHA into the red blood cell membrane fatty acids (a 160% increase from baseline) when compared to the EEs.[23]After six months, the increases in the n-3 index from baseline were significantly higher for rTGs (197%) compared to EEs (171%). This observation indicated more rapid and maximum increases in the n-3 index derived from rTGs, when compared to EEs.[22] In a subset of subjects from this study (150 dyslipidaemic statin-treated participants) who also received either rTG, EE or corn oil capsules, the n-3 index was significantly higher in the rTG group, when compared to the placebo and the EE group after both three and six months. No significant difference was reported for blood TG levels between the rTG and EE groups after both time intervals.[19]

Krill oil

Krill oil (KO) is a relatively new source of n-3 fatty acids. The bioavailability of KO is reportedly increased because of the esterification of n-3 fatty acids in PLs, rather than from TGs or EEs.[24] However, findings of recent clinical trials concerning the increased bioavailability of EPA and DHA from KO were not conclusive when compared to studies involving EPA and DHA bound to TGs. Maki et al[25] performed a randomised, double-blind clinical trial on 76 obese men and women over a four-week period. Participants received capsules with 2 000 mg/day KO (216 mg EPA and 90 mg DHA), menhaden oil (212 mg EPA and 178 mg DHA), or olive oil. No significant differences in the absorption of plasma EPA and DHA between the krill and menhaden oil groups were reported. Ulven et al[26] reported similar non-significant changes between plasma EPA and DHA for fish oil (864 mg total n-3 fatty acids) and KO (543 mg total n-3 fatty acids) in a randomised, parallel group clinical trial of seven weeks' duration. They compared the uptake of EPA and DHA between fish oil and KO in 113 healthy participants. It was concluded that both KO and fish oil represented comparable dietary sources of n-3 fatty acids. Schuchardt et al[19] administered 1 680 mg EPA and DHA in the form of rTGs, EEs or KO to 12 healthy young men. The fatty acid levels were analysed in plasma PLs prior to supplementation 2, 4, 6, 8, 24, 48 and 72 hours after supplementation. In general, the incorporation of EPA and DHA in plasma PLs was maximal with KO supplementation, followed by rTGs and EEs. Unfortunately, this study did not include fish oil in the TG form to be compared to rTGs and EEs.

Frequency of fish oil intake

Current research conducted by our group suggests that n-3 fatty acids need to be ingested continuously, preferably on a daily basis. In a randomised, controlled trial on healthy adults, 1 200 mg/day salmon oil was administered over a six-week loading period. It was observed that the disappearance rates of EPA from TGs, cholesterol esters and total PLs were dissimilar on termination of the loading period. With cessation of the loading period, 50% of the participants discontinued supplementation and a washout period of six weeks was implemented. The EPA demonstrated the most rapid disappearance rate from TG (half life (t½) = 3 days) and total PLs (t½ = 5.5 days) was the longest. After 21 days without supplementation, EPA levels in the TGs returned to baseline levels.[16] In red blood cells (RBCs), the disappearance rates of EPA from the phosphatidyl choline (PC) membranes were shortest (t½ = 5.5 days) when compared to the phosphatidyl ethanolamine membranes (t½ = > 7 days). The EPA levels in the PC membranes returned to baseline levels after 21 days.[27] Instead of following the washout period, the remaining 50% of the participants continued with 600 mg/day salmon oil. During the following six weeks, the n-3 fatty acid levels of these participants stabilised and were maintained at levels above the baseline. Measured dietary fat intake remained constant over the course of the trial. Considering the rapid disappearance rates of n-3 fatty acids from plasma lipids and RBCs, it is recommended that n-3 fatty acids should be taken on a regular basis to ensure that n-3 levels are maintained above baseline values in the blood.

It should be kept in mind that dietary fat is mainly ingested in the form of TGs. The TGs cannot be readily absorbed in the intestine. Instead, to ensure absorption, TGs must be converted to free fatty acids and monoglycerides in the presence of pancreatic lipase. In pure fish oil, EPA and DHA are bound to TGs and therefore also utilise lipases for absorption. For this reason, it is recommended that fish oil supplements should be consumed in combination with a fat-containing meal.

Labelling legislation

South African consumers have grown accustomed to the quality inherent in the manufacture of conventional medicinal products as stipulated by the Medicines Control Council. Usually, they accept the consistency, purity and potency of prescription and non-prescription medications and preparations without question. Consequently, consumers have little reason to doubt the package label claims on conventional medication. However, a similar claim cannot be made for dietary supplements since no regulatory structure for dietary supplements currently exists. The Foodstuff Cosmetics and Disinfectants Act No 54 of 1972 (Amendment No 39 of 2007)[28] does not supply any definitions for dietary or nutritional supplements, nor does the new Labelling and Advertising of Foodstuffs Regulations (R146),[29] published in 2010. Instead, dietary supplements are included in the wider-ranging definition of foodstuffs. While this definition is comprehensive for the description of a foodstuff, it does not explain explicit differences between foodstuffs and dietary supplements. Consequently, the requirements and procedures for the quality control, packaging, labelling and presentation of both dietary supplements and foodstuffs are identical.

Quality control needs to be addressed during the manufacturing, production and commercialisation of n-3 fatty acid supplements, as these should not be the same as that for foodstuffs containing n-3 fatty acids. In a recent first analysis in South Africa on the n-3 fatty acid content of 45 fish oil supplements available on the South African market, concerns were raised about the quality of these supplements. Analysis of the n-3 fatty acid content of fish oil supplements indicated that 51% and 56% of the EPA and DHA contents, respectively, were at levels lower than the levels reported on the supplement labels. In addition, the conjugated diene (CD) levels of the supplement oils were determined. The CD levels are an indication of early stages of rancidity. Elevated CD levels implicate deterioration in the quality of oils. The comparison of the CD contents of the supplement oils to those of unopened canola, sunflower and olive oil, revealed that more than 73% of the oils in the supplements displayed higher CD levels than the vegetable oils.[30]

N-3 fatty acids, in the form of supplements, appear to be the safer and more controllable way of consuming n-3 fatty acids. However, all preparations rely on fish oil as a source of EPA and DHA. Importantly, the n-3 fatty acid content of deep-sea oily fish, from which fish oil preparations are derived, is influenced by the geographic origin of the fish, as well as the season of harvest. Thus, the fatty acid content in fish varies significantly. Poor quality of raw materials, suboptimal storage conditions, as well as inconsistency in the potency and purity of fish oil, further contribute to the variability of the fatty acid content in fish oil supplements. As inconsistent fatty acid content in supplements may contribute to errors in daily dosage and associated unfavourable dose-related side effects, proper legislation is essential to ensure consistency in the n-3 fatty acid content of fish oil-derived supplements. Accurate information on supplement labels will empower the consumer to make an informed decision about the number of capsules that supply a certain dose of EPA and DHA, as well as aid them in choosing a supplement that will suit their lifestyle. Potential solutions would be to perform batch-by-batch analyses, accompanied by the provision of a certificate of analysis, on the n-3 fatty acid content of supplements. Ideally, these recommendations should be mandatory and enforced by appropriate legislation regarding the manufacture of all dietary supplements.

Because of the lack of appropriate legislation, many claims made by manufacturers of dietary supplements remain unchallenged. Companies that manufacture or distribute fish oil or fish oil combination supplements need to ensure the safety of these supplements by authenticating any representations or claims made on the product by means of relevant and evidence-based research. This would prevent claims that are both false and misleading. This evidence should be accessible to consumers. Consumers should also be made aware that even when implementing current good manufacturing practice guidelines during the production process, the safety of the product is not guaranteed. Separate regulations on purity, bioavailability, potency, possible adverse effects, safety aspects, active ingredients, allergies and contraindications of supplements should also be stipulated. A legislative body to address these issues should be created to ensure enforcement of the legislation.

Potential adverse effects

Although evidence-based research has confirmed that increased intakes of n-3 fatty acids are valuable for some health conditions, n-3 supplements should to be used with caution. Excess intakes of n-3 fatty acids in healthy populations may lead to undesirable side-effects, such as the suppression of the immune system, nose bleeds in individuals with hypercholesterolaemia, and prolonged bleeding time with increased risk of haemorrhagic strokes and increased levels of lipid peroxidation.[2] In addition, the simultaneous intake of n-3 fatty acids with anticoagulant medication, such as aspirin and warfarin, prolongs bleeding times in individuals using these medications. Currently, no supporting data exist to establish a safe upper limit for n-3 fatty acids. However, the US Food and Drug Administration has ruled that intakes of up to 3 g/day of marine n-3 fatty acids are "generally recognised as safe" for inclusion in the diet.[31]

A further concern is the effect of fish oil supplementation on lipoprotein cholesterol levels. Recent meta-analyses and systematic reviews[32] have reported that treatment with EPA or DHA showed diverse effects on high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol. Both treatments induced lower blood TG levels. However, DHA was more often associated with both elevated HDL cholesterol levels and increased LDL cholesterol levels. The increase in LDL cholesterol is undesirable. However, clinical trials elsewhere[33,34] have indicated that fish oil supplementation is associated with increased LDL cholesterol particle size, or a shift in LDL cholesterol particle distribution from small, dense particles to larger, less dense LDL cholesterol particles which are known to be less atherogenic.

General advice

Consumers are often confused as to which n-3 supplements to purchase. Since it has been reported that there is a limited conversion of plant-derived n-3 fatty acids to EPA and DHA, consumers are advised to purchase pure fish oil supplements, in which other additional fatty acids are absent. Many fish oil supplements are often combined with n-6 and n-9 fatty acids. As these two latter fatty acids are abundant in the Western diet, they should not be further supplemented. Current general recommended daily intakes of n-3 fatty acids are approximately 500 mg/day. Therefore, consumers should be advised to purchase supplements that contain these amounts. Excess fish oil consumption (> 3 000 mg/day) should be avoided. Supplement labels should clearly indicate the exact contents of both the fish oil supplement and the EPA and DHA contents in a capsule. Furthermore, the source of fish oil should be indicated. Health professionals could advise consumers to buy supplements from an outlet where they have not been stored on shelves for excessive periods of time where light exposure is a problem. Hence, consumers should avoid buying supplements that are packaged in clear containers since exposure to light may enhance the rancidity of the oils. Consumers are also advised not to use supplements beyond the expiry date. It is also not always the rule that the most expensive supplements represent optimum quality.

As indicated in the foregoing, fish oil supplements are not safeguarded against false and misleading claims. Consumers should scrutinise rare claims that are made on supplement labels. If claims sound too good to be true, they usually are! To promote a product, many supplement manufacturers make unsubstantiated claims on labels and increase product sales. This also undoubtedly benefits company research, development and competitiveness. Forged, misleading claims create idealistic expectations and waste money. Such unethical practices can cause an incorrect supplement dosage, thus leading to detrimental health effects. Several companies base their evidence on animal data which cannot be extrapolated to the human system. Supplement users should always vigilantly compare health claims with evidence-based research, or properly consult trained nutrition professionals. Consumers who are allergic to fish should avoid taking fish oil supplements. Preferably, supplements should be purchased from reputable companies that provide a certificate of analysis with proven quality control.

Finally, pregnant and lactating women must familiarise themselves with the contents of any n-3 supplement. Supplements are often sold as a combination of fish oil, amended with vitamins and/or minerals. Therefore, additional supplementation of the specific vitamin and/or mineral should be avoided to prevent overconsumption during pregnancy. A further concern is the EE content in n-3 fatty acid supplements. In a recent survey conducted by our group, it was discovered that a third of n-3 fatty acid supplements available on the South African market consist of EEs. Pregnant women are advised against the use of EEs since the safety of EEs during pregnancy has not been established. When EEs are converted back to TGs during digestion, alcohol is released. Even though the quantity of ethanol released in a typical dose of fish oil via supplementation is small, at-risk groups such as alcoholics, pregnant women and young children should refrain from using n-3 fatty acid supplements that contain EEs. The EEs of fatty acids has shown toxicity in vivo[35] and in vitro,[36] and is known to accumulate in major organs, such as the heart, liver, pancreas, and potentially the placenta.[37] In a rat study,[38] it was observed that efficient fatty acid EE digestion in the gastrointestinal tract may prevent toxicity. However, this was not confirmed in humans. At present, no manufacturers indicate the form (EEs, TGs and or rTGs) in which n-3 fatty acids are present in capsules.

Conclusion

Following a typical Western diet complicates the optimal dietary intake of EPA and DHA. Generally, it is believed that fish oil supplements are a safe and easy method of accomplishing favourable n-3 fatty acid intakes. However, several factors need to be considered when choosing a fish oil supplement. The bioavailability of EPA and DHA in TG, EE or rTG forms varies, and may be a concern as South African fish oil supplement labels do not specify the form of n-3 fatty acids present. From the literature, it appears that EPA and DHA, in the form of TGs, rTGs and PLs, are absorbed more efficiently, compared to the EE form. During digestion, EEs are converted back to TGs, while ethanol is released. The safety of fish oil supplements in the form of EEs has not been confirmed. Vulnerable groups, like alcoholics, pregnant women and young children, should refrain from taking EEs. It is recommended that fish oil supplements should be taken every 24-48 hours to ensure that n-3 blood levels are maintained above baseline. Taking n-3 fatty acid supplements in combination with a fat-containing meal may aid in improving absorption. Recent reviews reported the diverse effects of EPA and DHA on lipoprotein cholesterol. DHA was more often associated with an increase in LDL cholesterol and HDL cholesterol. Fish oil supplementation was associated with less dense, larger LDL cholesterol and HDL cholesterol particles which are cardioprotective.

Finally, the absence of a regulatory structure for dietary supplements is a major concern for South Africans. Such a regulatory structure is fundamental in protecting consumers against substandard supplements and false, misleading claims that might adversely affect their health. Therefore, South African health professionals should assist patients by obliging government to establish appropriate and mandatory legislation for all dietary supplements.

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