Maturitas 103 (2017) 71–77

Contents lists available at ScienceDirect

Maturitas

journal homepage: www.elsevier.com/locate/maturitas

Recommendations of the Spanish Menopause Society on the consumption of omega-3 polyunsaturated fatty acids by postmenopausal women

ARTICLE INFO

Keywords:
Omega-3 polyunsaturated fatty acids
Menopause
Cardiovascular disease

ABSTRACT

The consumption of long-chain omega-3 polyunsaturated fatty acids (LCO3-PUFAs) has shown a great variety of beneficial effects, including cardiovascular, metabolic and inflammatory effects, which make them interesting for the postmenopausal woman. Because LCO3-PUFAs could be effective and safe during this period, a panel of experts from the Spanish Menopause Society met to establish a set of recommendations for their use in postmenopausal women based on the best available evidence.

The decrease in triglycerides is the most consistent effect observed with LCO3-PUFAs (at doses greater than 3 g/day). In addition, LCO3-PUFAs have antiarrhythmic effects, reduce blood pressure, improve depressive and psychotic symptoms, and do not increase the risk of cancer. However, further studies are needed to confirm the benefit of LCO3-PUFAs in the relief of menopause symptoms and osteoporosis.

1. Introduction

The effects of long-chain omega-3 polyunsaturated fatty acids (LCO3-PUFAs) have been studied extensively in a wide variety of clinical situations due to the wide range of physiological functions in which they are involved. The regular consumption of LCO3-PUFAs is accompanied by general health benefits, highlighted by their cardiovascular, metabolic and inflammatory actions, which make them potentially beneficial for postmenopausal women [1].

Because LCO3-PUFAs could be effective and safe during this period, a panel of experts from the Spanish Menopause Society met to establish a set of recommendations for their use in postmenopausal women based on the best available evidence.

2. Methods

The Spanish Menopause Society considers it appropriate to develop its own recommendations based on the GRADE (*Grading of Recommendations Assessment, Development and Evaluation*) system to clarify clinical practice guidelines and to classify the quality of the evidence and the strength of the recommendations [2].

To obtain the present set of recommendations we searched the MEDLINE, EMBASE, PubMed, Scopus and Cochrane databases for all articles (in any language) published in peer-reviewed journals through March 2017 using the search strategy described in Appendix A. Reference lists from papers identified by the search, as well as key reviews, were hand-searched to identify additional publications. Those that were in press in peer-reviewed journals and available online, ahead of publication, were also considered. Full articles that met the inclusion criteria were reviewed in detail. Other relevant papers were searched for References

3. Long-chain OMEGA-3 polyunsaturated fatty acids

As essential fatty acids with important metabolic and structural functions, LCO3-PUFAs are not synthesized by the human body; rather, they must be obtained from the diet. The consumption of products of marine origin is a source of LCO3-PUFAs (see types and sources in Table 1) with vasodilator, anticoagulant and anti-inflammatory effects [3].

Other important essential fatty acids are omega-6s, which come mainly from meat and vegetable oils and demonstrate actions contrary to those of LCO3-PUFAs. The balance between intake of one or another type of essential fatty acids has been directly or indirectly related to health. The consumption of omega–6 s far exceeds the recommendations established in most European countries, while that of the LCO3-PUFAs falls short [4].

Because of the beneficial effects with which it has been associated, a daily intake of 250 mg of LCO3-PUFAs is recommended, which could be achieved with two or three weekly servings of fish or shellfish. Although blue fish contains the most LCO3-PUFAs, it is also associated with the highest concentrations of mercury; thus, it is prudent to control its consumption. Because of this risk and because fish stocks are insufficient in the environment, supplementation of intake of LCO3-PUFAs, for example eicosapentaenoic acid (EPA) plus docosahexaenoic acid (DHA), with fish, algae

http://dx.doi.org/10.1016/j.maturitas.2017.06.028
Received 19 May 2017; Received in revised form 17 June 2017; Accepted 22 June 2017

Table 1
Dietary sources of the main long chain omega-3 polyunsaturated fatty acids.

alpha linoleic acid (ALA)	VEGETABLE SOURCES: flax seeds, soybeans; nuts and oils of linseed, soybean, pumpkin seeds, rapeseed, camelina seeds, chia seeds, among others.
eicosapentaenoic acid (EPA)	MARINE ORIGIN: krill, blue fish (salmon, mackerel, herring, sardines, anchovies, tuna, etc.).
docosahexaenoic acid (DHA)	MARINE ORIGIN: algae, blue fish, krill.

or krill oils is recommended. Those that come from fish oils are in the form of triglycerides, and vitamin E is added to prevent their oxidation. In krill oil, however, EPA + DHA are in the form of phospholipids, which have higher absorption, functionality and distribution than triglycerides and are less prone to oxidation. In addition, krill oil contains astaxanthin, a potent antioxidant [5].

4. Cardiovascular effects

Both regular consumption of fish and LCO3-PUFAs supplementation at a dose of 250 mg/day have been associated with a lower risk of cardiovascular death in both healthy adults and patients with cardiovascular disease (CVD). In general, a fish-rich diet (more than 2 servings per week) is recommended for the general population and for those with CVD because fish provides LCO3-PUFAs while replacing less heart-healthy protein sources (red meat) [6–8]. However, we do not have conclusive evidence from randomized controlled trials (RCTs) and observational studies to recommend the supplementation of EPA + DHA in the prevention of CVD.

In a meta-analysis of 2012, LCO3-PUFAs supplementation was not associated with a lower risk of all-cause mortality (relative risk [RR] = 0.96, 95% CI: 0.91–1.02; risk reduction [RD] = 0.004, 95% CI: −0.01 to 0.02), cardiac death (RR = 0.91, 95% CI: 0.85–0.98; RD = −0.01, 95% CI: −0.02 to 0.00), sudden death (RR = 0.87. 95% CI: 0.75–1.01; RD = −0.003. 95% CI: −0.012 to 0.006), myocardial infarction (RR = 0.89, 95% CI: 0.76–1.04; RD = −0.002, 95% CI: −0.007 to 0.002), and stroke (RR = 1.05, 95% CI: 0.93–1.18; RD = 0.001, 95% CI: −0.002 to 0.004) when all supplement studies were considered [9].

In a systematic review and meta-analysis [10], the RR for cerebrovascular disease was related to a low ingestion of LCO3-PUFAs and fish. In the cohort studies, the RR of cerebrovascular disease for persons eating 2–4 portions of fish per week was 0.94 (95% CI, 0.90–0.98), and the RR for persons eating more than five portions a week was 0.88 (95% CI, 0.81–0.96). In the RCTs, the RR for cerebrovascular disease was 0.98 (95% CI, 0.89–1.08) with LCO3-PUFAs supplement in primary prevention trials, and 1.17 (0.99–1.38) in secondary prevention trials. However, the cerebrovascular benefit of fish consumption is probably due to the abundant variety of nutrients in fish [10].

In individuals with peripheral arterial disease, a meta-analysis showed that there was insufficient evidence of a beneficial effect of LCO3-PUFAs supplementation on cardiovascular events (pooled risk ratio 0.73, 95% CI, 0.22–2.41) [11].

In patients with impaired glucose metabolism, consumption of LCO3-PUFAs had no statistically significant effect on cardiovascular mortality, major cardiovascular events, all-cause mortality or a composite endpoint of all-cause mortality or hospitalization for CVD, but it significantly reduced the level of triglycerides (mean difference 0.25 mmol/L; 95% CI −0.37 to −0.13: $p < 0.001$; 12 trials, 13,921 patients) [12].

The role of LCO3-PUFAs for primary prevention of CVD was analyzed in a global consortium of 19 studies. Their consumption was associated with a modestly lower incidence of fatal coronary heart disease (CHD) (RRs of 0.91–95% CI, 0.84-0.98- for ALA, 0.90–95% CI, 0.85-0.96- for DPA, and 0.90–95% CI, 0.84–0.96- for DHA) [13].

Recently, assessing the efficacy of EPA dietary supplements in the primary prevention of cause-specific death, CVD, and cancer by using meta-analytical approaches, no significant risk reduction for any of the outcomes was found [14].

Consequently, we do not have conclusive evidence to recommend the use of EPA + DHA supplements in the prevention of CVD. Recent studies show conflicting data, and little evidence is available regarding cardiovascular events other than coronary heart disease. Accordingly, studies with adequate sample sizes are required that also consider the individual baseline level of LCO3-PUFAs and the time of supplementation.

4.1. Omega-3 fatty acids status

In all trials, participants were recruited based on clinical inclusion and exclusion criteria that did not account for baseline LCO3-PUFAs status [15]. Recruiting study participants irrespective of baseline LCO3-PUFAs results in a large proportion with a high baseline status that are unlikely to benefit from EPA + DHA supplements. This dilutes the effects of EPA + DHA on clinical endpoints in the entire study population [16].

In addition, the bioavailability of EPA + DHA in capsules is minimal if they are taken with a low-fat meal. However, if taken with a high-fat meal, the bioavailability of EPA + DHA increases by up to 13-fold [17]. The positive result of the trial conducted according to the advice to eat fatty fish supports the relevance of the bioavailability issue [18].

In bioavailability studies in humans, it was learned that the increase in omega-3 fatty acid status from a given dose of EPA + DHA shows large inter- and intra-individual variability [18,19]. Nonetheless, if trials in populations characterized by low levels of omega-3 fatty acids were analyzed, a positive effect might be shown with EPA + DHA.

This argument highlights the clinical relevance of omega-3 fatty acid status. Omega-3 fatty acid status is best determined in erythrocytes (low biological variability of omega-3 fatty acids) and with a standardized analytical method, that has very low variability [15]. The “HS-Omega-3 Index®”, associated with 168 publications in international journals, comprises the largest database of all comparable analytical methods. The HS-Omega-3 Index presents the percentage of EPA + DHA in erythrocytes, but 26 fatty acids are measured. Other laboratories analyze fatty acid compartments with high biological variability, have unspecified analytical variability, and/or have no scientific database. It is therefore not surprising that, even if erythrocytes are analyzed, the results of other methods vary by up to a factor of 3.5. Based on the large database, a target HS-Omega-3 Index range of 8–11% has been suggested [15]. Large proportions of populations in Korea and Japan have been found in this target range, and Japan and Korea have minimal rates of cardiovascular disease. In Europe and Canada, however, large proportions of the populations studied have been found below the target range. Assessing diet does not predict an individual’s HS-Omega-3 Index. By increasing intake of EPA + DHA, the