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A Journey through ω-3 Supplements: Future Perspectives for Precision Nutrition

Iker Jauregibeitia, Kevin Portune, Javier Amezaga, Itziar Tueros, Sara Arranz*

Basque Research and Technology Alliance (BRTA), Parque Tecnológico de Bizkaia,
Astondo Bidea, Edificio 609, 48160 Derio (Bizkaia), Spain
*Corresponding author: sarranz@azti.es

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Abstract Increasing evidence has shown that fatty acids play a key factor in nutrition and health. Despite the well described health benefits associated to the omega-3 fatty acids (ω-3 FA) intake from epidemiological and clinical trials, controversial results are found from some clinical trials regarding the effect of ω-3 FA supplementation to handle certain diseases. In this review, we provide orientation for the reader to understand the importance of a personalized recommendation of the ω-3 polyunsaturated fatty acid supplementation based on a precision nutrition approach. We begin by reviewing the metabolic relevance of ω-3 fatty acids and then discuss the current state of ω-3 fatty acid supplements regarding their indications, regulation, variety from brand to brand, adverse effects and the need to implement a personalized supplementation. We conclude with future perspectives for practitioners and general guidance on precision nutrition.

Keywords: *lipidomics, omega 3 fatty acids, precision nutrition, health*

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1. Introduction

In the last decades, omega-3 fatty acids (ω-3 FA) supplements have experienced a growing increase in consumption by the general public, becoming an increasingly important part of the diet [1]. For example, the use of ω-3 supplements among adults in the U.S. has increased from 4.8% in 2007 to 7.8% in 2012 [2]. The factors that explain this increase in consumption, among others, are the more scientifically backed evidences on the beneficial health effects of ω-3 FA [3] and the fact that typical current dietary habits in western countries do not meet the recommended amount of ω-3 FA intake that should be used for optimal health conditions [4].

2. Metabolic Relevance of ω-3 Fatty Acids

ω-3 FA are essential fatty acids that must be obtained from the diet because humans and other mammals lack endogenous enzymes to synthesize them. Alpha-linolenic acid (ALA) is the precursor of the metabolic pathway for ω-3 FA and can be found in green leafy vegetables and in some seeds (flax, rape, chia, perilla and walnuts). Even if mammalian cells are not able to synthesize ALA, they can metabolize it into more physiologically active compounds by a set of desaturating enzymes via Δ5 and Δ6 desaturases and by lengthening the acyl chain (elongation) via elongases, thus converting them into longer-chain fatty acids of 20 and 22 carbon atoms [5].

Metabolically speaking, the most important ω-3 FA are EPA (20:5 ω-3) and DHA (22:6 ω-3), which have been associated with numerous health benefits. Adequate consumption of ω-3 FA, mainly EPA and DHA fatty acids, has been proven to be vitally important for fetal and infant development [6], improved cardiovascular health [7], benefits in cancer by promoting tumor cell apoptosis [8], immune system [9], or a decreased inflammatory response to injury [10], among other benefits.

Although EPA and DHA can be synthesized from shorter plant-derived ω-3 FA precursors such as ALA, this metabolic pathway is not efficient in humans. Approximately only 8-20% of ALA is converted to EPA in humans, while conversion of ALA to DHA is estimated to be around 0.5-9% [11], although this rate may be affected by hormones [12], sex [13], genetics [14] and age [15]. In addition, since several enzymes are shared between the metabolic pathways of ω-3 and ω-6 PUFAs, ω-3 and ω-6 substrates compete for access to these enzymes and this competition is highly influenced by the relative ratios of each type of PUFA. Furthermore, the ratio of ω-6:ω-3 FA is highly affected by dietary intake and is found in excess of ω-6 in many Western countries (i.e. 20:1 ω-6:ω-3 compared to the 1:1 ratio during evolution), due to increased consumption of the linoleic acid (LA), a precursor of the ω-6 metabolic pathway that is rich in vegetable oils [16]. For example, consumption of LA in the U.S. according the U.S. Department of

Agriculture has increased 8 times for men and 6 times for women from the beginning of the XIX century to nowadays [17].

An added problem lies in the fact that long chain ω-6 and ω-3 PUFAs synthesized from LA and ALA not only have different, but often opposing effects on immunity and inflammation. Arachidonic acid, which is the main long chain ω-6, metabolites promote acute and chronic inflammation acting as local hormones. In contrast, EPA and DHA can be metabolized to anti-inflammatory mediators [18].

This illustrates the importance of a sufficient dietary intake of EPA and DHA to provide enough levels of ω-3 FA for optimal human health.

3. Indications for ω-3 Fatty Acid Intake

Currently, different recommendations are given by associations and government organizations regarding the dosage of ω-3 FA for the maintenance of optimal health conditions or alleviation of possible disease states. For example, in the UK, the recommendation of ω-3 FA intake is at least two fish meals per week including at least one meal consisting of oily fish (i.e. salmon, tuna, anchovies, sardines etc..), in which translates to an EPA+DHA recommendation of around 450 mg/day [19]. In France, the official recommendation for ω-3 FA intake is 400-500 mg/day of EPA+DHA with at least 100-120 mg/day DHA [20]. The Superior Health Council of Belgium recommends a minimum of 1-2% energy from ω-3 FA for adults, with at least one oily fish per week to supply 250 mg/day of EPA+DHA [21]. The Health Council of the Netherlands establishes a weekly consumption of one serving of fish, preferably oily fish, for a target quantity of 225 mg/day of EPA+DHA [22]. The target intake for Australia and New Zealand is 160 mg/day EPA+DHA for men and 90 mg/day for women [23]. The European Food Safety Authority and the Dietary guideline for Americans, from the U.S. Department of Agriculture and the Department of Health and Human Services, point out that as the available data on ω-3 FA intake is insufficient to derive an average requirement, an intake of 250 mg per day of EPA+DHA appears to be sufficient for cardiovascular prevention in healthy subjects [24,25]. The World Health Organization recommends regular fish consumption (one to two servings per week; each serving should provide the equivalent of 200-500 mg of EPA+DHA) [26].

Differences in ω-3 FA intake recommendations are reflected in differences in the actual average intake of EPA and DHA between countries with western diets [27]. For example, a nationally representative cross-sectional survey collected by the National Center for Health Statistics of the Centers for Disease Control and Prevention in the U.S. showed that the intake of DHA and EPA from foods and dietary supplements for adults was 72 ± 4 mg/d and 41 ± 4 mg/d, respectively [28]. The average consumption of ω-3 FA in Canada is around 177 mg/day, in Australia around 143 mg/day , and in many parts of Europe the daily intake of EPA + DHA by adults is <100 mg/d, since many never eat oily fish [29].

Regarding this, the European Food Safety Authority (EFSA) reported different health benefits associated to daily intake of ω-3 FA that can be included as health claims in manufactured food labeling [30].

A recommended dietary allowance for the optimum minimum intake of EPA and DHA ω-3 FA is therefore needed for the general population without considering any disease state or other specific requirement in special situations (i.e. pregnancy, sports performance) that could potentially alter the recommended amount of each respective fatty acid.

At the same time, there is not a current consensus regarding the tolerable upper intake level (UL) for ω-3 supplements due to insufficient data. Different recommendations have been established in different countries. For example, Australia, New Zealand, and The US Food and Drug Administration set a reference value for the UL of EPA+DHA at 3 g/d [26]. Meanwhile, EFSA states that long-term supplemental intakes of combined EPA and DHA up to 5 g/day do not appear to increase the risk of adverse side effects such as spontaneous bleeding episodes or bleeding complications, or lipid peroxidation among others [4].

4. Regulation of ω-3 Supplements

Since dietary supplements are widely available to the general public (i.e. they are not over-the-counter drugs and are not regulated as such), their purity, chemical integrity, efficacy and safety remains unverified [31]. Some studies show that the concentration of ω-3 FA were lower than what it was stated in the supplemental labels [32] and contained higher oxidation levels than what was permitted by current legislation [33]. In this sense, lipid peroxides contribute to accelerate oxidation of other fatty acids leading to lipid membrane peroxidation, cell damage, and oxidative stress [34]. Endogenous membrane lipid peroxidation results in altered membrane fluidity, transport, and cell signaling [35].

At the same time, levels of trans-isomers have been measured in different concentrations [36] likely due to the high temperatures and pressures used during the manufacturing of concentrated supplements [37]. The dietary intake of trans-fatty acids (TFA) has adverse effects on blood lipid levels, because they cause an increase on LDL-cholesterol and a decrease on HDL-cholesterol [38], both well-established markers of cardiovascular disease [39]. Similarly, cohort studies demonstrated that high intake of TFA is associated with an increased coronary heart disease and mortality rates [40,41].

Current product formulations of ω-3 supplements are offered in various options, ranging from soft gels (most common) to liquids, powders, and gummies, with oil sources from fish, krill, algae and plants. The quantities and prices of ω-3 FA found in dietary supplements are highly variable within and between brands. The dosage recommendations for ω-3 consumption by different manufacturing brands also largely differs, even for recommendations for the treatment of the same disease. For example, Figure 1 shows a comparison of the recommendations of the daily intake of EPA, DHA and

EPA+DHA for treating cholesterol from 10 different commercial ω-3 supplement products that authors have selected from available products in the European market. This comparison reveals large differences between the recommended doses of supplements from one brand to another, leading to an increased confusion in consumer choice for selecting the adequate supplemental dosages.

ω-3 FA in supplements can be found in different forms such as triglycerides, free fatty acids, ethyl esters and phospholipids. Bioavailability of ω-3 PUFAs as phospholipids (as it appears mainly in krill oil) is higher than other forms of ω-3s [42], while triglycerides and free fatty acids have higher bioavailability than ethyl esters [43]. This is another feature that must be considered when deciding between the appropriate supplement for personal use.

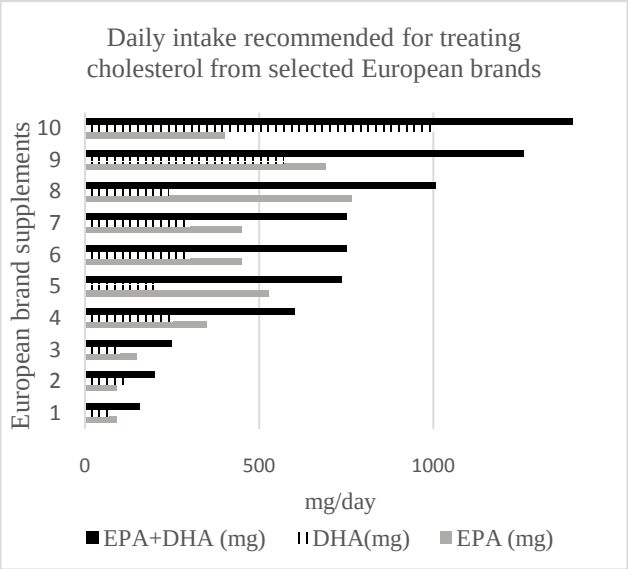

Figure 1. Daily EPA+DHA intake recommended for treating cholesterol from selected European brands

5. Personalized Supplementation

Due to the controversy regarding specific recommendations of adequate intake of ω-3 for the general population as well as different population sub-groups (i.e. those with diet-related diseases), personalized ω-3 intake strategies should be adopted. Implementation of new omic tools, such as genomics, metabolomics, proteomics and transcriptomics, to the field of precision nutrition can facilitate detailed information on specific genotypes as well as the current levels of proteins and metabolites, thus enabling the identification of metabolic deficiencies or genetic variations within individuals. Hence, information obtained from these technologies can lead to a more precise personalized nutritional recommendation by providing information on different responses to diets, on dietary intake, and on new early biomarkers of certain diseases [44], all of which should be considered for recommendations of adequate dosage for each individual.

Examples of applying targeted-omic tools to asses ω-3 supplementation include studying the effect of PUFAs on genetic variation via epigenetic modifications [45] or the study of different metabolomic and transcriptomic profiles of responders and non-responders of ω-3 supplementation [46].

Cell membrane lipidomics, a specific sub-group within metabolomics, offers analyses of long-term food consumption and metabolism history: cell membrane composition reflects the absorption efficiency of the ingested fatty acids, metabolism and distribution of the resulting molecules [47,48]. Cell membrane lipidomic monitoring can also be applied to large populations allowing the molecular characterization of specific diseases or health risk factors, such as, diabetes mellitus [49], cardiovascular disease [50], obesity/overweight, cancer, allergies/intolerance [51]. By determining the actual levels of cell membrane fatty acids of an individual, innovative nutritional strategies to improve health status can be designed, including diet and specific supplements targeting different population groups to help consumers to properly choose the adequate fatty acid supplementation among commercially available products according to their specific needs.

Controversial results from ω-3 supplementation trials can be found in the literature for patients with cardiovascular disease [52]. One reason that ω-3 supplementation was not beneficial in these studies may be due to the fact that they did not measure the basal and endpoint ω-3 FA levels [53,54], therefore it is impossible to determine the actual changes in ω-3 levels in these patients. This further supports the application of lipidomic tools to these studies in order to assess the potential benefits of ω-3 FA supplementation.

6. Conclusions

It can be concluded that the intake of ω-3 supplements is a useful way to reach the recommended levels of ω-3 FA when the current dietary habits don´t meet these demands, especially in cases where higher levels may be required (i.e. disease, pregnancy, infant development). Nevertheless, more research should be carried out in the field to establish an adequate recommended dietary allowance for ω-3 FA in order to provide a clear message to the general public.

However, in the current situation where more research is leading to individualized health and nutritional recommendations, the use of omic technologies for a more precise and personalized supplementation appears to be crucial in order to achieve the expected health benefits and to allow consumers to make correct choices for their needs concerning dosage or different fatty acid supplements. This is not a trivial issue because the supplements are at the reach of any consumer, without any control, and when they are consumed in excess or for long-term, can negatively impact health.

In this sense, the application of cell membrane lipidomics provides a valid option to understand the structural and functional changes in fatty acid composition in both normal and pathological states. It also provides a measurement of the specific fatty acid needs for each individual based on their basal metabolic levels, as well as different metabolic changes that occur supplementation.

Future perspectives should focus as well on the effectiveness of different ω-3 FA sources for supplements

(marine and vegetable oils) and how new industrial processes can affect the quality of these supplements.

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Competing Interests

None of the authors have any competing interest.

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List of Abbreviations

ALA: Alpha-linolenic Acid; **DHA:** Docosahexaenoic Acid; **EFSA:** European Food Safety Authority**; EPA:** Eicosapentaenoic Acid; **FA:** Fatty Acids; **LA:** Linoleic Acid; **MUFA:** Monounsaturated Fatty Acids; **PUFA:** Polyunsaturated Fatty Acids; **SFA:** Saturated Fatty Acids; **TFA:** Trans-Fatty Acids**; UL:** Upper intake Level; **ω-3:** Omega 3.

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