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Review

Omega-3 long chain fatty acid "bioavailability": A review of evidence and methodological considerations

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ABSTRACT

This review considers the bioavailability of different forms of omega-3 long chain polyunsaturated fatty acids (n-3 LC-PUFA), including ethyl esters (EEs), free fatty acids (FFAs), triacylglycerols (TAGs) and phospholipids (PLs). The retrieved studies include short-term and longer-term studies in humans, and a number of animal studies, which were highly heterogeneous in their design making it difficult to draw substantiated conclusions. The apparent bioavailability (as defined by the authors of these studies) seems to be lowest for the EE form and highest for the FFA form, whilst no conclusion can be made for TAG versus PL from human data. Animal studies suggest that there are substantial differences in the bioavailability of PL form of LC-PUFA compared with the TAG form. This apparent limited knowledge and understanding is fundamentally driven by methodological limitations of these studies. The major limitations with the studies to date include: (between studies) loose definition of the term "bioavailability", lack of standardisation of analytical methodology, and differences in which blood compartment was analysed; (within a study) failure to provide equal amounts the n-3 LC-PUFA of the different forms being compared, failure to provide the dose of n-3 LC-PUFA on a body weight basis, failure to measure fatty acid excretion, failure to control the total fat intake, and failure to adequately power the studies from a statistical point of view. This review has laid out a set of suggestions and criteria for conducting future studies on the bioavailability of different chemical forms of n-3 LC-PUFA.

Contents

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1. Introduction

Omega-3 long chain polyunsaturated fatty acids (n-3 LC-PUFA) are highly unsaturated fatty acids which are particularly abundant in fish and other seafood. There are three main n-3 LC-PUFA: eicosapentaenoic acid (EPA; 20:5n-3), docosapentaenoic acid (DPA; 22:5n-3) and docosahexaenoic acid (DHA; 22:6n-3); however, since there has been relatively little research on DPA [1], this review will focus on EPA and DHA. In the last five decades, it has been well documented by a plethora of studies that the ingestion of EPA and DHA can improve health and in some instances can contribute to preventing disease. Therefore, various national and international health authorities have made recommendations for n-3 LC-PUFA dietary intakes, which range from 250 mg per day up to 2 g per day of EPA plus DHA [2,3]. In Australia, the daily required intake for healthy adults of approximately 500 mg of n-3 LC-PUFA has been recommended by National Health and Medical Research Council of Australia; whilst the American Heart Association recommendation for patients with coronary heart disease (CHD) is 1 g EPA plus DHA per day, and for patients with high plasma triglyceride levels, the recommendations range from 2 to 4 g EPA plus DHA per day [4]. The European Society of Cardiology recommended 1 g of EPA plus DHA for secondary prevention of CHD [5]. However, the ingestion of a given quantity of n-3 LC-PUFA does not directly correlate with the actual quantity of n-3 LC-PUFA available for the body. As with all nutrients, the rate n-3 LC-PUFA digestion, absorption, excretion and retention in tissues (i.e. n-3 LC-PUFA bioavailability) can differ for n-3 LC-PUFA differently esterified (i.e. contained in different chemical macromolecules).

Dietary supplements of n-3 LC-PUFA are widely available, and these are commonly in triglyceride (TAG; natural sources typically derived from fish oil) form, in free fatty acid (FFA) form, or in ethyl esters (EEs) form, with both of the latter forms being derived from natural sources of fish oil TAG. More recently, krill oil derived sources, which contain a significant portion of their n-3 LC-PUFA in phospholipids (PLs) and FFA form, are also increasingly found on the market, and marketed as being of "higher efficacy", compared with traditional n-3 LC-PUFA supplements.

The commercial interest in n-3 LC-PUFA dietary supplements has been fuelled by the almost overwhelming number of published studies on the potential effects of dietary n-3 LC-PUFA. However, and quite surprisingly, little scientific attention has been paid to the actual bioavailability of n-3 LC-PUFA in various dietary supplements. This observation generated the initial impetus for this review paper, but at time of writing it, the first review paper by Schuchardt and Hahn on the topic of bioavailability of n-3 LC-PUFA was published [6]. This elegantly presented review paper focused primarily on the sources and chemical forms of n-3 LC-PUFA, and the possible mechanisms responsible for different bioavailability values observed for different chemical forms of n-3 LC-PUFA. As concluded by the authors, the information available thus far is not fully clear and mixed results have been reported. Another comprehensive review which compliments the present review is that by Michalski et al. [7] which considered in detail the influence of multiscale food/lipid structures (molecular and supramolecular) structures on fatty acid bioavailability and lipid metabolism.

As a result, we chose to adopt a different approach to our review by focussing on methodological considerations of studies on bioavailability of omega-3 fatty acids, specifically in humans, but considering also relevant information available from animal studies. Thus the aims of this paper were to (i) review the available scientific literature and knowledge relative to the bioavailability of n-3 LC-PUFA, when supplied in different chemical forms, (ii) summarise the existing evidence of possible differences in bioavailability; and (iii) carefully analyse the strengths and the limitations of these studies, paying specific attention to methodological considerations.

The ultimate objective of this study was to complement the information provided by Schuchardt and Hahn [6], and then suggest specifically tailored future methodological and analytical approaches to be used when assessing the bioavailability of n-3 LC-PUFA dietary supplements in humans – an area of research that clearly deserves a much more focused and substantiated scientific effort.

2. Literature search; methods and results of selected studies

To retrieve the relevant studies to be used in this review paper, a search strategy using Medline/PubMed, ScienceDirect, Web of Science, EMBASE was conducted using the following search terms: bioavailability, long chain fatty acids, omega-3, DHA, EPA, formulation, omega-3 index, fish oil, krill oil, capsule, and matrix. Subsequently all retrieved studies were analysed by carefully reading the full-text articles.

Of the 21 human studies reviewed, 4 articles were eliminated because they did not include a control group. Seventeen studies which reported on the association between bioavailability and n-3 LC-PUFA formulations in humans were selected.

A total of 8 studies were found as postprandial or short-term trials of up to 72 h and reported hereafter as Case Studies 1 to 8, respectively:

- El Boustani et al. [8], Case Study 1; study length 24 h;
- Lawson and Hughes [9], Case Study 2; study length 12 h;
- Lawson and Hughes [10], Case Study 3; study length 8 h;
- Beckerman et al. [11], Case Study 4; study length 32 h;
- Nordoy et al. [12], Case Study 5; study length 24 h;
- Wakil et al. [13], Case Study 6; study length 24 h;
- Schuchardt et al. [14], Case Study 7; study length 72 h;
- Davidson et al. [15], Case Study 8; study length 24 h;

Nine longer-term studies were found which ranged in length from two weeks to six months reported hereafter as Case Studies 9 to 17, respectively. Of these nine studies, only 2 studies analysed red blood cell membranes (RBC) and the remainder analysed either serum/plasma fatty acid or whole blood; thus, direct comparison between these longer-term studies is difficult.

- Reis et al. [16], Case Study 9, study length 6 months;
- Krokan et al. [17], Case Study 10, study length 2 weeks;
- Hansen et al. [18], Case Study 11, study length 7 weeks;