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Controversies in omega-3 efficacy and novel concepts for application

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ABSTRACT

Interest in the cardioprotective effects of long chain omega-3 polyunsaturated fatty acids (LCn3) was largely influenced by the low rates of cardiovascular disease (CVD) amongst the Inuits of Greenland who consumed a high marine fat diet rich in LCn3s. This finding stimulated years of epidemiological and clinical studies investigating the cardioprotective effects of LCn3s, thought to be primarily mediated through anti-inflammatory (and anti-aggregatory) prostaglandins that protect the vascular wall from pro-inflammatory effects of metabolic stress precipitated by poor diet and lifestyle. Although the original hypothesis of the link between LCn3s and CVD protection was based on a high LCn3 containing diet (namely a high marine fat diet) the majority of clinical trials since have focussed on EPA and DHA supplementation, and results of repeated meta-analyses have not shown conclusive evidence in support of their beneficial health effects. In this review we focus on the controversies that surround the efficacy of LCn3s in cardiovascular and other chronic diseases and present emerging areas of research for novel applications. We will examine factors that can impact on the efficacy of LCn3s such as source (plant vs marine vs supplements (algal vs marine)), stability of product, dose, trial duration, ratio of EPA:DHA, and ratio of LCn6:LCn3 fatty acids in the diet.

Contents

Abbreviations: CVD, Cardiovascular disease; AA, Arachidonic Acid; DHA, DocosaHexaenoic Acid; EPA, EicosaPentaenoic Acid; LCn3, Long Chain omega-3 polyunsaturated fatty acids; LCn6, Long Chain omega-6 polyunsaturated fatty acids; RCT, Randomized Control Trial.

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1. Introduction

Research on the beneficial aspect of LCn3s was prompted by the remarkably low rate of cardiovascular disease (CVD) amongst the Inuits of Greenland. A series of studies conducted on Inuits showed that despite consuming a high marine fat diet, the people had extremely low levels of Coronary Heart Disease (CHD) [1]. Interestingly, diabetes was essentially unknown in the population as compared to the Danish population living in Denmark [2]. The Inuits exhibited lower serum LDL-cholesterol and triglycerides, higher HDL-cholesterol and higher levels of LCn3 eicosapentaenoic acid (EPA) to LCn6 arachidonic acid (AA), compared to their Danish counterparts. Since this observation, a large number of experimental and clinical studies have demonstrated the health benefits of long chain n-3 PUFAs, however not all studies have been consistent. Bang and colleagues [3] hypothesised that eicosapentanoic acid (EPA) plays a crucial role in lowering the incidence of atherosclerosis, coronary heart disease and diabetes. In particular, the presence of EPA in the walls of the blood vessels instead of AA was reported to create an anti-thrombotic state that lowered the incidence of coronary heart disease amongst the Inuits [2]. This work has since been supported by a substantial body of evidence. In addition to this, researchers demonstrated that prostaglandins derived from LCn6 had increased pro-inflammatory activity compared with those derived from LCn3. Furthermore, studies suggested that EPA and docosohexanoic acid (DHA) derived from LCn3 are structurally and functionally distinct from the prostaglandins that are derived from AA. Marine plants and fish are the two main sources of dietary LCn3 [4]. The most concentrated source of LCn3 comes from fatty fish such as salmon, tuna and mackerel. LCn3s are incorporated into the cell membrane, thereby modulating cellular signalling, gene expression and membrane protein function. Dietary supplementation of LCn3 is known to promote secretion of anti-inflammatory prostaglandins and decrease leukotrienes [5]. These anti-inflammatory properties are thought to be beneficial in cardiovascular diseases and metabolic syndrome disorders such as central obesity, insulin resistance, hypertension and dyslipidemia [6,7]. Over the last decade, an increasing amount of experimental evidence suggests a crucial role played by DHA on neurodegenerative conditions such as mild cognitive impairment (MCI) [8,9] and Alzheimer's Disease [10].

While most epidemiological evidence and randomized control trials (RCTs) indicate the protective role of LCn3 on general health and wellbeing, there are some RCTs that have shown no effect [11]. The aims of this review are to evaluate (a) the evidence of the beneficial effects of LCn3 on various disease conditions such as metabolic syndrome and cardiovascular disease (b) discuss why some RCTs may not have positive outcomes, (c) highlight controversies in LCn3 efficacy and (d) identify emerging areas for LCn3 application as therapeutic agents.

2. Source of LCn3s: diet versus supplementation

Since the initial interest sparked by the Inuit studies, there has been a vast amount of research into the area of dietary fish intake, LCn3 supplementation and disease prevention and treatment. Controversy exists, however, as to whether LCn3 intake is responsible for benefits seen, whether fish intake itself is beneficial, or if fish intake is merely a marker for a healthier dietary pattern. The evidence for diet versus supplementation in different disease states should be considered and will be reviewed in this article.

(i) Diet versus supplementation - CVD events

Epidemiological support for the protective effect of fish is illustrated by the concept of the blue zone diets. So-called 'blue zones' are areas of the world where populations experience longevity (>100 years of age or more) and reduced morbidity compared to other populations [12]. Notable blue zone areas include the islands of Ikaria and Sardinia in the Mediterranean and Okinawa in Japan, with these areas having a high dietary intake of LCn3 amongst other dietary patterns. Fish is the major source of LCn3 intake in Japan and there are many examples of epidemiological support for a high LCn3 intake from fish, such as the Nurse's Health Study and the Chicago Western Electric Study which demonstrated an inverse relationship between fish consumption and mortality, particularly from CVD events [13–15]. Paradoxically, some epidemiological studies, show no relationship between LCn3 intake from fish and mortality [16] or that fish consumption is only protective in high risk groups [17].

Following on from the 'blue zone' diet concept there was interest in the use of supplemental LCn3 in cardiovascular disease, with significant reductions reported for secondary prevention of myocardial infarction [18]. Additionally, the Diet and Reinfarction Trial (DART) is an example of an RCT demonstrating that both fish consumption and dietary LCn3 supplementation could reduce mortality in the 2 years post-myocardial infarction [19]. Another study by Brazionis and colleagues [20], however, showed that fish consumption rather than fish oil improved risk factors of CVD such as blood pressure and waist to hip ratio. Controversy also exists in regards to how different CVD risk factors are impacted by fish oils. There is evidence supporting dietary supplementation with LCn3 fish oil in management of high triglycerides with meta-analyses showing a positive benefit on triglycerides with dietary supplementation [21], with certain populations receiving the most benefit including those with chronic renal disease or HIV positive populations receiving Highly Active Antiretroviral Therapy (HAART) [22]. A recent meta-analysis by Wei and Jacobson [23] compared the effects of supplementation of DHA and EHA concluding that both DHA and EPA lower triglycerides, with divergent effects on LDL and HDL cholesterol. Cardioprotective dietary patterns such as a Mediterranean style diet or a 'blue zones' type eating pattern include a wide variety of plant foods consumed with high levels of antioxidants and other bioactive nutrients that may act in a protective and synergistic way, increasing the quality of fatty acids incorporated into tissues.

(ii) Diet versus supplementation - Cognitive function

The role of LCn3 have also been examined in relation to cognitive function. Once again the current evidence suggest that certain populations may benefit more than others and different LCn3 may be important. A prospective cohort study by Morris and colleagues [24] demonstrated an inverse relationship between DHA and total LCn3 intake in older people, with no protective effect seen with EPA. Intervention trials have so far failed to support a role for supplementation to improve cognitive function in those with Alzheimer's Dementia [25] and with mixed results reported in healthy individuals [26,27]. A possible theory behind the conflicting and lack of positive results of supplement trials is the oxidisable nature of fish oil supplements which may reduce the bioavailability.

(iii) Diet versus supplementation - Fatty liver disease

An example illustrating the complexity of this research area is in fatty liver disease studies. A recent meta-analysis by Parker et al. [28] examined the role of LCn3 supplementation in reducing liver size. This was stimulated by previous research that showed patients with Non-Alcoholic Fatty Liver Disease (NAFLD) had habitually low consumption of fish compared to individuals without NAFLD