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Review

Omega-3 fatty acids and cardiovascular disease: A case for omega-3 index as a new risk factor

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Abstract

The omega-3 fatty acids (FAs) found in fish and fish oils (eicosapentaenoic and docosahexaenoic acids, EPA and DHA) have been reported to have a variety of beneficial effects in cardiovascular diseases. Ecological and prospective cohort studies as well as randomized, controlled trials have supported the view that the effects of these FAs are clinically relevant. They operate via several mechanisms, all beginning with the incorporation of EPA and DHA into cell membranes. From here, these omega-3 FA alter membrane physical characteristics and the activity of membrane-bound proteins, and once released by intracellular phospholipases, can interact with ion channels, be converted into a wide variety of bioactive eicosanoids, and serve as ligands for several nuclear transcription factors thereby altering gene expression. In as much as blood levels are a strong reflection of dietary intake, it is proposed that an omega-3 FA biomarker, the omega-3 index (erythrocyte EPA + DHA) be considered at least a marker, if not a risk factor, for coronary heart disease, especially sudden cardiac death. The omega-3 index fulfils many of the requirements for a risk factor including consistent epidemiological evidence, a plausible mechanism of action, a reproducible assay, independence from classical risk factors, modifiability, and most importantly, the demonstration that raising tissue levels will reduce risk for cardiac events. For these and a number of other reasons, the omega-3 index compares very favourably with other risk factors for sudden cardiac death.

Keywords: Eicosapentaenoic acid; Docosahexaenoic acid; Biomarkers; Risk factors; Cardiovascular disease; Coronary heart disease; Sudden cardiac death; Fish oils

Contents

1. Introduction

The American Heart Association [1], the European Society for Cardiology [2], the Scientific Advisory Committee on Nutrition (UK) [3], the Australian Health and Medical Research Council [4] and a host of other health agencies

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and professional organizations have issued recommendations for increased intakes of omega-3 fatty acids (FAs). These recommendations are based on strong evidence derived from a variety of scientific approaches linking dietary deficiency of long chain omega-3 FAs with risk for cardiovascular events, notably sudden death. These have been recounted in detail in several recent publications [1,5–11]. The primary purpose of this paper is to make a case for the use of a biomarker for omega-3 FA intake, "the omega-3 index," in coronary heart disease (CHD) risk stratification. In so doing, the results of omega-3 epidemiological and interventional studies, and their apparent mechanisms of action will be briefly reviewed.

2. Omega-3 epidemiology

In order to summarize the fish/omega-3 ecological studies, He et al. [12] performed a meta-analysis of 13 cohorts including over 222,000 individuals followed for CHD death for an average of about 12 years. They found that the consumption of only one fish meal per week (versus <1 per month) was associated with a statistically significant 15% reduction in risk. When subjects were classified into categories of increasing fish consumption (<1/month, 1–3/month, 1/week, 2–4/week, and ≥5/week), those in the highest intake group enjoyed a 40% reduction in risk. Similar findings were reported for stroke [13].

An inverse relation between fish intake and risk for CHD has also been recently reported in Greek [14] and in Japanese cohorts [15]. The latter study examined the association between fish (and omega-3 FA) intake and various CHD endpoints in 41,578 Japanese men and women age 50–70 over a 10-year follow-up period. The lowest quintile of intake was about 300 mg/day, which is about twice the median intake in the US [16]. At the high end, intakes averaged 2.1 g/day. The median intake in this cohort was about 900 mg/day, about six-fold higher than US intakes. Across this intake gradient there was a significant reduction in risk for non-fatal coronary events and total myocardial infarctions (Fig. 1). Hence, the intake of omega-3 FA at which benefits plateau is not yet defined.

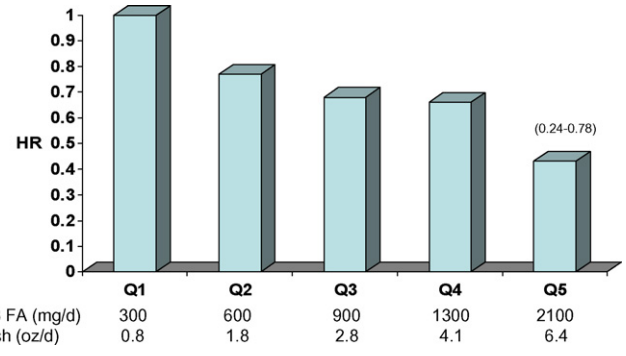

Fig. 1. Risk for MI by median omega-3 FA intake estimated from reported fish intake in the Japan Public Health Center-Based Study Cohort I. 41,578 subjects; 40–59 years; 10 year f/u. Age, sex, smoking, alcohol, BMI, Hx HTN and diabetes, drug use for elevated cholesterol, educational level, sports in leisure time, and quintiles of dietary fruits, vegetables, sat fat, mono fat, $n-3$ fat, cholesterol and kcal. p for trend = 0.02. Adapted from Iso et al. [15].

3. Omega-3 interventions

There have been several intervention studies of varying quality (see references [7,11]). The largest and most well controlled was the GISSI Prevenzione study, which tested the hypothesis that relatively small intakes of omega-3 FA (<1 g) could reduce risk for death from CHD in high risk patients. Over 11,000 post-myocardial infarction patients were randomized to either one capsule of omega-3 FA ethyl esters (Omacor, Pronova Biocare, Norway; 850 mg of EPA + DHA) or usual care and then followed for 3.5 years. In this study, the risk for death from any cause was reduced by 20% and risk for sudden death by 45% in the supplement group [17].

To bring a perspective to the beneficial effects of omega-3 FA, Studer et al. [18] computed the relative reduction in risk for death from any cause in trials of anti-lipidemic drugs and lipid-lowering diets. These regimens are obviously prescribed not just to reduce serum lipid levels, but ultimately to reduce risk for death, typically from CHD. Over 137,000 patients receiving treatment for lipid disorders were compared to controls in a total of 97 studies. There were 35 trials with statins, 7 studies with fibrates, 8 with bile acid binding resins, 14 with omega-3 FA and 18 examining the effects of global dietary changes. Only two interventions were associated with significant reductions in total mortality: statins (risk ratio 0.87, 95% CI 0.81–0.94) and omega-3 FA (risk ratio 0.77, 95% CI 0.63–0.94). Although a fascinating analysis that underscores the fact that risk for serious adverse health outcomes can be reduced even without lowering cholesterol, one could argue that two studies included with the omega-3 group were not strictly omega-3 studies but overall dietary interventions. In these two studies [19,20], the active agent(s) cannot be identified with confidence because so many dietary variables differed between groups. Whether removing these studies from the omega-3 group would leave the latter still associated with reduced risk for death is not clear. Nevertheless, the preponderance of the data suggests that for most individuals, increasing the intake of long-chain omega-3 FA is a safe and inexpensive way to significantly reduce risk for CHD, especially sudden cardiac death.

4. Omega-3 mechanisms

The fundamental mechanism by which omega-3 FA appear to mitigate risk for CHD begins with the enrichment of membrane phospholipids with EPA and DHA. Once these long chain omega-3 FA are resident in cell membranes, they may have at least four separate effects. The relative importance of each, their coordinated interaction and their sufficiency to explain the clinical observations have yet to be determined.

First, because of their highly unsaturated nature, they may alter membrane properties [21]. This can have the secondary effect of changing the microenvironment of transmembrane proteins (e.g., receptors) altering the manner in which they interact with their ligands [22]. Altering membrane FA composition can also affect the ability of membrane-associated proteins to actually associate with the membrane and consequently to interact