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Reprint of: Marine OMEGA-3 fatty acids in the prevention of cardiovascular disease

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ABSTRACT

Omega-6 (ω6) and omega-3 (ω3) fatty acids are two classes of dietary polyunsaturated fatty acids derived from linoleic acid (18:2ω6) and α-linolenic acid (18:3ω3), respectively. Enzymatic metabolism of linoleic and α-linolenic acids generates arachidonic acid (20:4ω6) and eicosapentaenoic acid (20:5ω3; EPA), respectively, both of which are substrates for enzymes that yield eicosanoids with multiple and varying physiological functions. Further elongation and desaturation of EPA yields the 22-carbon fatty acid docosahexaenoic acid (22:6ω3; DHA). The main dietary source of EPA and DHA for human consumption is fish, especially oily fish.

There is considerable evidence that EPA and DHA are protective against cardiovascular disease (heart disease and stroke), particularly in individuals with pre-existing disease. ω3 Fatty acids benefit multiple risk factors including blood pressure, blood vessel function, heart function and blood lipids, and they have antithrombotic, anti-inflammatory and anti-oxidative actions. ω3 Fatty acids do not adversely interact with medications. Supplementation with ω3 fatty acids is recommended in individuals with elevated blood triglyceride levels and patients with coronary heart disease. A practical recommendation for the general population is to increase ω3 fatty acid intake by incorporating fish as part of a healthy diet that includes increased fruits and vegetables, and moderation of salt intake. Health authorities recommend the general population should consume at least two oily fish meals per week.

1. Introduction

Observational studies from more than forty years ago showed the Greenland Inuit population had a low incidence of coronary artery disease and a reduced prevalence of arthritis, psoriasis, asthma and diabetes, that most likely related to their lifestyle and in particular to their distinctive diet [1–3]. The Greenland Inuit diet derived mainly from cold water fish and artic mammals such as seal and whale. It contained higher protein and fat, lower carbohydrates and significantly greater amounts of omega-3 (ω3) polyunsaturated fats, particularly eicosapentaenoic acid (EPA, 20:5ω3) and docosahexaenoic acid (DHA, 22:6ω3), rather than omega-6 polyunsaturated fats such as linoleic acid (18:2ω6) and arachidonic acid (20:4ω6) that are characteristic of the Western diet [2]. The plasma fatty acid profile of the Inuit population was consistent with these differences in dietary fats. They had a more favourable lipid profile, typically lower in triglycerides, cholesterol, low density lipoprotein cholesterol (LDL-C) and very low density lipoprotein cholesterol (VLDL-C), and higher in high density lipoprotein cholesterol (HDL-C). They also had reduced blood clotting and thrombosis [1–3].

2. Sources, biochemistry and metabolism of ω3 and ω6 fatty acids

ω6 and ω3 Fatty acids represent two classes of polyunsaturated fatty acids that derive from linoleic acid (18:2ω6) and α-linolenic acid (18:3ω3), respectively (Fig. 1). The nomenclature for the ω6 and ω3 fatty acids relates to the presence of a double bond at the sixth or third carbon, respectively, from the methyl terminus of the fatty acid chain. Metabolism of linoleic and α-linolenic acids by desaturase and elongase enzymes generates arachidonic acid and EPA, respectively. Both arachidonic acid and EPA are substrates for cyclooxygenase, lipoxygenase and cytochrome P450 enzymes, yielding eicosanoids and mediators of inflammation resolution with multiple and varying physiological functions. Further metabolism of EPA yields the 22-carbon fatty acid DHA. There are numerous reports that the eicosanoids derived from EPA are generally less biologically active than those from arachidonic acid [4], or they antagonise the action of those metabolites derived from arachidonic acid [5].

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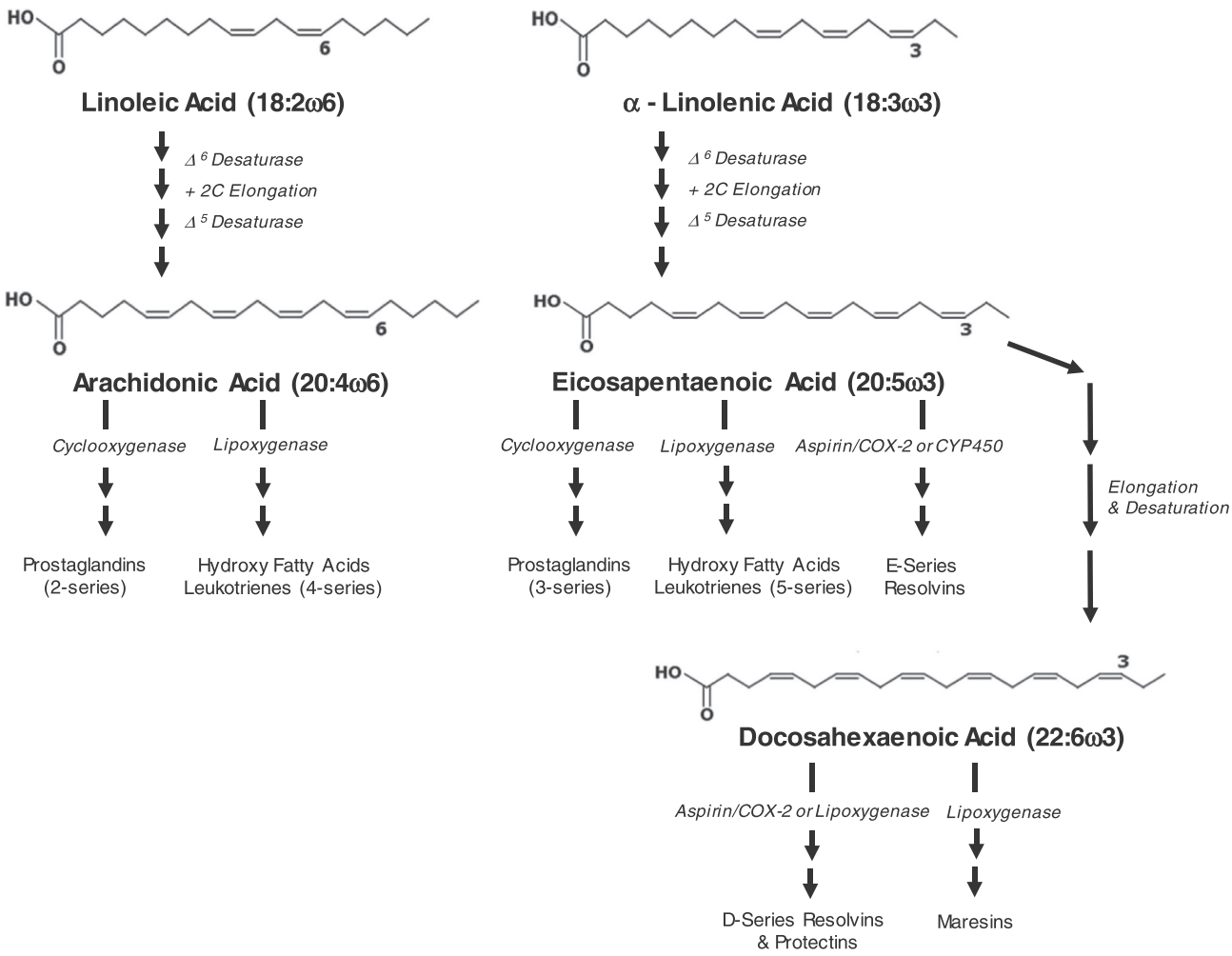

Fig. 1. Metabolism of linoleic acid and a-linolenic acid to arachidonic acid and eicosapentaenoic acid, respectively. Both arachidonic acid and eicosapentaenoic acid are substrates for cyclooxygenase, lipoxygenase and cytochrome P450 enzymes, yielding eicosanoids and lipid mediators of inflammation resolution. Eicosapentaenoic acid is further elaborated to docosahexaenoic acid.

Western diets are generally more abundant in ω6 fatty acids that are found mainly in vegetable oils rich in linoleic acid. The dietary intake of α-linolenic acid, found in plant oils such as linseed oil (~53%), canola oil (~10%), soybean oil (~7%) and walnut oil (~10%), is relatively low. Humans are unable to pre-form linoleic acid and α-linolenic acid, and thus these fatty acids are termed "essential" dietary fatty acids. Humans are also unable to convert ω6 fatty acids to ω3 fatty acids and have a very limited capacity to convert α-linolenic acid to EPA and DHA [6]. Thus, the main dietary sources of EPA and DHA are fish especially oily fish such as mackerel, salmon, cod, mullet, herring and flounder.

3. Evidence from population studies

A number of population studies and meta-analyses have examined the relationship between ω3 fatty acids and cardiovascular disease [7–15]. In a meta-analysis comprising 15,806 patients, Bucher et al. [7] showed that ω3 fatty acids associated with a 30% reduction in fatal myocardial infarction and sudden death ($P < 0.01$), and a 20% reduction in overall mortality ($P < 0.001$). Whelton et al. [10] in 19 studies comprising 228,864 participants, showed that fish consumption associated with a risk reduction of 17% for fatal coronary heart disease (CHD) ($P < 0.005$) and 14% for total CHD ($P < 0.005$). A meta-analysis by He et al. [8] that included 222,364 individuals, showed the relative risk for CHD mortality was reduced by 23% in those that ate fish 2–4 times/week, compared with individuals who either never ate or consumed less than one fish meal per month.

Two recent meta-analyses by Maki et al. [15] and Alexander et al. [14] assessing use of EPA and/or DHA supplements provide additional support that these fatty acids confer benefits on cardiovascular health. In an analysis of 14 randomised controlled trials including 71,899 subjects, Maki et al. [15] reported an 8.0% ($P = 0.015$) lower risk for cardiac death with ω3 fatty acids versus controls. A meta-analysis by Alexander et al. [14] that included 8 randomised controlled trials and 16 prospective cohort studies incorporating 732,000 individuals examined EPA + DHA from foods or supplements and CHD, including myocardial infarction, sudden cardiac death, coronary death, and angina. The data showed that among randomised controlled trials there was a non-significant 6% reduction in CHD risk with EPA + DHA. However, subgroup analyses indicated a statistically significant CHD risk reduction with EPA + DHA among higher-risk populations, including participants with elevated triglyceride levels (16% reduction) and elevated low-density lipoprotein cholesterol (14% reduction). Meta-analysis of data from prospective cohort studies showed a statistically significant 18% reduction for higher intakes of EPA + DHA and risk of any CHD event. However, not all meta-analyses have shown benefits of ω3 fatty acids on cardiovascular outcomes [16–18]. Rizos et al. [18] reported ω3 fatty acids did not associate with a lower risk of all-cause mortality, cardiac death, sudden death, myocardial infarction or stroke, in a meta-analysis of 20 studies and 68,680 patients. The