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Marine oils: Complex, confusing, confounded?

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ABSTRACT

Marine oils gained prominence following the report that Greenland Inuits who consumed a high-fat diet rich in long-chain n-3 polyunsaturated fatty acids (PUFAs) also had low rates of cardiovascular disease. Marine n-3 PUFAs have since become a billion dollar industry, which will continue to grow based on current trends. However, recent systematic reviews question the health benefits of marine oil supplements, particularly in the prevention of cardiovascular disease. Marine oils constitute an extremely complex dietary intervention for a number of reasons: i) the many chemical compounds they contain; ii) the many biological processes affected by n-3 PUFAs; iii) their tendency to deteriorate and form potentially toxic primary and secondary oxidation products; and iv) inaccuracy in the labelling of consumer products. These complexities may confound the clinical literature, limiting the ability to make substantive conclusions for some key health outcomes. Thus, there is a pressing need for clinical trials using marine oils whose composition has been independently verified and demonstrated to be minimally oxidised. Without such data, it is premature to conclude that n-3 PUFA rich supplements are ineffective.

1. Introduction

In 1971, Bang and Dyerberg reported low rates of cardiovascular disease in Greenland Inuits who consumed a fatty diet made up almost exclusively of oily fish and seal meat, a paradox given the contemporary understanding of the association between dietary fat and cardiovascular disease [1]. While this observation has recently been questioned [2], it sparked considerable scientific interest. Since then, a vast scientific literature has emerged exploring the health effects of marine oils rich in n-3 polyunsaturated fatty acids (PUFAs), in particular the long chain eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Alongside, a billion dollar industry has arisen [3], marketing fish oil and other marine oils to consumers, such that marine oils are now one of the most popular supplements worldwide [4]. In the USA, they are used by 6.5% of the population (37% of supplement users) [4] and 8% of college students [5]. In a study in New Zealand, 15% of women undergoing fertility treatment were taking marine oil supplements [6].

In many ways, scientists and physicians have approached marine oils as they would a medication, investigating their health effects using randomised controlled trials, with controlled doses, for specific indications. Marine oils have a long list of apparent indications, including prevention of cardiovascular disease [7] and cognitive decline [8], improvement of infant neurodevelopment [8], and treatment of inflammatory diseases such as rheumatoid arthritis and asthma [9]. Recommended doses differ depending on indication [9,10], and products are labelled so that consumers can determine a target dose of n-3 PUFAs.

However, there is increasing evidence to suggest that marine oils are actually ineffective for secondary prevention of cardiovascular disease, which is their highest profile indication [11,12]. In reality, marine oil supplements are quite unlike medications in many respects, including the complexity of their biological effects, their impurity (containing many chemical compounds), the inaccuracy of labelled content, their potential to degrade to toxic compounds, and limited regulation of sales and marketing. Consideration of the complexity of marine oils and the ways they differ from typical drugs may help explain why they appear not to have delivered on the promising tale of the Greenland Inuits.

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2. n-3 PUFA actions

There is a very large range of physiological effects associated with n-3 PUFAs, which is quite unlike most medications.

2.1. Anti-inflammatory

They inhibit inflammatory processes at 5 distinct levels:

1) Increasing cell membrane fluidity, which interferes with activation of immune cells such as T-lymphocytes [13].
2) Activating the transcription factors PPAR-α [14] and PPAR-γ [15], and the transmembrane receptor GPR-120 [16], which inhibit the proinflammatory NF-κB pathway [17–19]. This reduces the production of inflammatory cytokines such as TNF-α and IL-6 and cell adhesion molecules such as ICAM and VCAM [9].
3) Competing with n-6 PUFAs as a substrate for the COX-2 enzyme, shifting the balance of eicosanoids from the proinflammatory n-6 series to the anti-inflammatory or less inflammatory n-3 series [9].
4) Competing with n-6 PUFAs as a substrate for endocannabinoid synthesis, which leads to the production of anti-inflammatory endocannabinoids [9].
5) Forming protectins and resolvins which have a role in ending the inflammatory response [9].

2.2. Lipid metabolism

n-3 PUFAs also have important effects on lipid metabolism through interaction with key transcription factors. They activate PPAR-α [14] and inhibit SREB1-c [20] and HNF-4α [21] in the liver. The combined effect is to increase fatty acid β-oxidation for energy production and reduce lipid synthesis [20,22], reduce hepatic fat storage [14,23], and limit the release of triglycerides into the circulation [14,23]. PPAR-γ is a key regulator of adipose tissue function that is also activated by n-3 PUFAs [23]. Activation of PPAR-γ increases adipogenesis [24], up regulates enzymatic pathways involved in uptake and storage of lipid [25] and insulin signalling [26], inhibits free fatty acid release, and normalises adipokine production [27]. It is noteworthy that the activation of PPAR-γ is the primary mechanism for the insulin-sensitising effects of thiazolidinediones, which are used in the management of diabetes mellitus [26].

2.3. Redox status

While n-3 PUFAs function as antioxidants [28], their impacts on biological systems are complex. Their participation in redox reactions leads to the production of a lipid peroxide radical, which itself is highly reactive [29]. In one study, lower doses of n-3 PUFAs had an antioxidant effect, but higher doses (≥1600 mg/day) were associated with increased markers of oxidative damage [30]. Aside from dose, many other factors are likely to influence the redox effect of n-3 PUFAs, including the degree to which the oil was oxidised prior to consumption, the concentration of antioxidants in the oil, and the endogenous antioxidant status of the consumer. Further, as obesity, inflammation, infection, and hyperglycaemia all influence oxidative stress [31,32], many aspects of health may modulate the redox effects of marine oils.

2.4. Central nervous system

DHA is a major structural component of the central nervous system and the retina, making up 35% of fatty acids within synaptic membranes [33]. There is rapid uptake of DHA in late gestation [34] and infancy [35], and deficiency is associated with cognitive defects in animal models [36]. Supplementation with n-3 PUFAs has been investigated as a treatment for a wide range of neurological and psychiatric disorders, and they are frequently taken during pregnancy or infancy with the aim of improving neurodevelopment [6,8].

n-3 PUFAs also have anti-arrhythmic properties [37], and like any fatty acid can be stored in adipose tissue or undergo β-oxidation for energy production.

2.5. Diversity of effects

As outlined above, n-3 PUFAs have a wide diversity of effects through many different mechanisms. Whilst it could be assumed that these are synergistic, some of these effects may be conflicting.

Ferrannini observed that medications that have a very specific action (affecting a single metabolic pathway) are usually preferable, because unintended/unpredicted adverse effects are less likely [38]. The statins (a class of drugs that reduce synthesis of cholesterol by inhibiting the enzyme HMG–CoA reductase) are a good example [38]. In contrast, the thiazolidinediones act through PPAR-γ, which is expressed in many tissues, and has many transcriptionally-regulating actions [26]. While these drugs do have important insulin sensitising effects, reports have shown an increased risk of congestive heart failure [39] and fractures [40]. From this perspective, marine oils, which affect many pathways in addition to PPAR-γ, have greater potential for unpredictable and potentially adverse effects.

Importantly, the multiple mechanisms by which n-3 PUFAs modulate inflammation and metabolism may also make it harder to translate the results of animal studies to humans. To standardise between species, doses are often considered adjusted for weight or body surface area [41]. This is reasonable if there is only one mechanism of action, as if there are differences in the affinity of enzymes or receptors for a drug or compound of interest, these are likely to differ by a constant factor, which may simply change the required dose to achieve a biological effect. However, when there are multiple distinct biological effects, such as for n-3 PUFAs, it is possible that the activity through each mechanism could vary by a different factor. In that case, the overall effect in different species would be very difficult to predict. Notably, the insulin-sensitising effects of marine oils have not clearly translated from rodents [16] to humans [42].

3. Marine oils contain more than n-3 PUFAs

The n-3 PUFAs EPA and DHA are considered to be the active compounds in marine oils, and the typical labelled content is between 300 and 600 mg/g of oil. However, marine oils also contain significant quantities of monounsaturated and saturated fatty acids, as well as small amounts of n-6 PUFAs. Further, in addition to fatty acids, there are other chemical species, including fat-soluble vitamins, carotenoids, phospholipids, cholesterol, and glycerol. In fact, two recent clinical trials that presented an independently measured fatty acid profile of the trial oil showed that the fatty acid content was only 42% of the oil mass in a krill-salmon blended oil [43] and 75% in a fish oil [44].

Oils made from krill are becoming an increasingly popular source of n-3 PUFAs. These oils may contain an even wider range of chemical components as the fatty acids are in the form of phospholipids [45,46], which have water-soluble and lipid-soluble poles. Thus, krill oils may also contain water-soluble molecules. In a randomised controlled trial of krill-salmon blended oil, supplementation lead to reduced insulin sensitivity, which was unlikely to