Review

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From alga to omega; have we reached peak (fish) oil?

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Summary

While the Inuit diet was highly cardio-protective and consuming oily fish within a Western diet is to a lesser degree, the case for purified fish oil supplements is less convincing. Purification of fish oil removes lipophilic polyphenols which likely contribute to the health benefits of oily fish; leaving the ω3 highly unsaturated fatty acids exposed and prone to conferring oxidative and inflammatory stress. The authors believe that due to such issues as dietary shift, it may now be inadvisable to prescribe or sell purified ω3 highly unsaturated fatty acids supplements, unless the appropriate co-factors are included.

Keywords

Fish oil, HUFA, polyphenol, phlorotannin, secoiridoid, Inuit, Mediterranean

Introduction

Despite early observations about the healthy nature of the Inuit diet, recent clinical trials and meta-analyses of fish oil supplements have failed to show convincing benefits. The authors believe that this discrepancy is due to a combination of poor formulation, and a deterioration in dietary omega 6:3 ratios. Evidence is adduced to support this hypothesis.

Methods

This is a narrative review and is not intended to be exhaustive. It attempts to frame a series of questions about the therapeutic use of purified fish oils. Research was primarily initiated via PubMed and Google Scholar and included retrieving a timeline of the most important prospective randomised controlled trials and meta-analyses of fish oils, and ω3 papers in the top tier biochemistry and food chemistry journals. Analytical and logistical data were requested from independent laboratory facilities and other industrial sources.

The Inuit diet vs Fish Oil

There is little doubt that traditional diets high in ω3 highly unsaturated fatty acids were healthy diets. In the late 1970s, pioneering Danish researchers Hans Olaf Bang and Jørn Dyerberg found that the Inuit, whose diet consisted mainly of meat and blubber of seal and whale with relatively small amounts of oily fish, were substantially protected against cardiovascular disease and had very low rates of most of the diseases now thought to be caused/driven by chronic inflammation. The Danes showed that this protection was related to the ω3 highly unsaturated fatty acids in the Inuit's food.[1–4] Many studies subsequently supported Bang and Dyerberg's ideas, and ω3 highly unsaturated fatty acids became the poster child for improved health through nutrition. A recent Harvard study which calculated that ω3 deficiency was killing 96,000 Americans per year[5] drove awareness even higher.

Today, millions of health-conscious consumers swallow purified and deodorised fish oil, mostly in capsules, in the belief that these products encapsulate the Inuit diet and will help keep them healthy. Their faith in fish oil supplements may, however, be misplaced.

One lesser known aspect of Inuit dietary habits is that they traditionally consumed the bulk of their food raw or dried; it was seldom cooked or exposed to excessive heat.[a] Most sophisticated urbanites would rather swallow purified, deodorised fish oil capsules than spend their evenings chewing raw whale meat and seal blubber, but highly processed fish oil capsules are a long way from the Inuit diet, and there is emerging evidence that under certain circumstances they may do more harm than good.

Too Pure to be True?

Edel Elvevoll, Bjarne Østerud and colleagues at the University of Tromsø have shown that the industrial processes typically used to extract and purify fish oil destroy or remove the trace ingredients in fish (such as algal-derived lipophilic polyphenols) that cause organoleptic and cosmetic problems for supplement manufacturers – but which likely also played a critical role in conferring the health benefits of the Inuit diet.

Removing these trace compounds reduces the ω3 highly unsaturated fatty acids anti-inflammatory effects,[6] presumably partly via the imposition of oxidative stress/ω3 peroxidation.[7–14] In certain situations such as heavy exercise,[8] high purified ω3 highly unsaturated fatty acids intakes,[10,11,13] insufficient antioxidant cover[8,9] and significant pre-existing oxidative stress and/or inflammatory pathology,[8,13] this may create a pro-inflammatory environment, manifesting *inter alia* with increased DNA damage[9] and increased levels of soluble vascular cell adhesion molecule (sVCAM-1).[13] It is important to point out that others have found sVCAM-1 to be reduced;[15] the divergent findings may reflect different intakes of dietary ancillary factors in different populations.

There is some evidence that older mice and men, many of whom take purified fish oil supplements, are intrinsically more vulnerable to the ω3 highly unsaturated fatty acids potentially pro-inflammatory effects.[9,16–18] While the elderly well and well-nourished may be adequately protected and thus able to enjoy the benefits of ω3 highly unsaturated fatty acids supplements,[16] the pre-existence of inflammatory pathology and related oxidative stress, which is more prevalent in older subjects and in those who eat a poor diet,[17–20] may be a contraindication to supplementation with purified ω3 products.[21,22] The last of these categories is perhaps the most concerning, as there are many who take fish oil capsules in an attempt to compensate for a poor diet. What implications might this have for the clinical application of ω3 highly unsaturated fatty acids?

Even the most ardent ω3 supporters would have to concede that since the early successes of DART-1 and GISSI, the results of clinical trials have been mixed. DART-2, a prospective study of 3114 men aged under 70 years with angina was a disappointment.[23] Men advised to eat oily fish, and particularly those supplied with fish oil capsules, had a higher risk of cardiac death, although aspects of the trial design weaken the significance of these findings.[24] A subsequent large meta-analysis[25] found that supplements of ω3 capsules were not associated with a lower risk of all-cause mortality, cardiac death, sudden death, myocardial infarction or stroke based on relative and absolute measures of association. There were also null or at best marginal results in the admittedly disparate JELLIS,[26] GISSI-HF,[27] ALPHA-OMEGA,[28] OMEGA,[29] SU.FO.OM,[30] ORIGIN[31] and CART[32] trials.

The argument is by no means closed. A powerful four-year prospective cohort study found higher circulating individual and total ω3 highly unsaturated fatty acids levels to be associated with lower total mortality, especially CHD death, in older adults;[33] this was in adults obtaining ω3s from fish rather than supplements, and who were, therefore, also consuming algal polyphenols. It is also conceivable that fish consumption was a proxy for a generally better diet. An alternative meta-analysis of adults taking ω3 supplements[34] did, however, find an association with reduced mortality and cardiac events.

On balance, eating oily fish still appears to have some effect in reducing all-cause and coronary heart mortality, although the data are somewhat less convincing for men who are free of cardiovascular disease,[35] so there is an emerging argument for eschewing supplements and going back to eating wild salmon, herring and mackerel, if not whale and seal. But there may be a problem here too; some scientists believe that due to pollution issues, eating fish is not as cardio-protective as it used to be,[36,37] and recent events at Fukushima will likely add to this argument. It also plausible that due to historically low calorific throughputs and dietary shift,[38] our intakes of key dietary antioxidant co-factors including the lipophile polyphenols are now so low that consuming higher levels of ω3 highly unsaturated fatty acids, even in fish, may expose us to more oxidative and, therefore, inflammatory stress.[14]

Classical antioxidants out-performed by source-appropriate protective compounds

Using purified fish oils is a valid way of reducing the burden of possible toxicants such as mercury, PCBs, etc. and a preferred strategy may be to combine purified fish oils with the appropriate co-factors. Vitamin E, the antioxidant most commonly used in fish oil capsules, does not appear to be an optimal candidate. It may protect the oils while they are in the capsule, but it does not necessarily protect them once they have been consumed. Supplementing the diet with purified ω3 fatty acids can increase lipid peroxidation, as measured by plasma MDA release and lipid peroxide products, and this is not suppressed by vitamin E supplementation.[14]

Promising alternative antioxidants include lipophilic polyphenols such as the secoiridoids and phlorotannins. Unlike many of the hydrophilic polyphenols, the olive compounds have excellent bioavailability.[39] This was recognised by an EFSA-approved health claim that that a mere 5 mg/day of secoiridoids was sufficient to protect LDL cholesterol from oxidative damage.[40] The phlorotannins are less well documented but in view of their broadly similar physico-chemical properties are likely to be similarly well absorbed; physiological changes including anti-hypertensive effects have been reported in clinical trials at doses of 100 mg/day.[41] Further investigations including formal bioavailability studies are currently

being coordinated by the EU-funded SWAFAX group, chaired by Professor Ian Rowland,[42] but until these are published, I am forced to lean on the more extensive olive data.

Once olive polyphenols enter the blood they become integrated into the lipoproteins which carry cholesterol and other lipids round the body and protect the lipoproteins including their lipid components from oxidation.[43–47] At the same time, they target the artery walls where they exert anti-inflammatory effects including the inhibition of the tissue-destructive MMP group of enzymes.[45–50] This is a powerfully cardio-protective strategy, and when combined with ω3 highly unsaturated fatty acids, the two sets of actives provide a potent anti-inflammatory, anti-atherogenic and cardio-protective environment.[50]

The olive polyphenols are now regarded as playing a key role in the health-promoting benefits of the Mediterranean diet.[43–50] It seems probable that the phlorotannins played an analogous role in the Inuit diet; indeed, lipophilic polyphenols appear to be the only major component that exists in both of these very disparate but mutually health-protective (and anti-inflammatory) diets. Their lipophilic nature also favours partitioning into adipose tissue, where they appear to inhibit the formation of pro-inflammatory adipocytokines.[51]

Detailed chemical analyses of unprocessed whale and seal oils are scarce. It is known, however, that unprocessed whale oil is typically a very pale brown in colour; and accounts of seal oil preparation involving rendering for five days at about 40°F indicate surprising stability, considering its highly unsaturated fatty acids content. These data strongly suggest that whale or seal meat and blubber, as it occurred in the Inuit diet, was rich in ancillary compounds that protected it against oxidation, as evidenced in the traditional Inuit health outcomes. Marine carotenoids, tocopherols and tocotrienols do not match the colour of unprocessed whale oil nor do they provide adequate anti-oxidant cover,[52] and it is likely that its brown colouration is due to (brown) phlorotannins derived originally, via multiple trophic levels, from brown marine algae.[b]

It is noteworthy that in *in vitro* models of oxidative stress, lipophilic polyphenols such as secoiridoids are the only compounds which provide antioxidant cover long enough to allow ingested ω3 highly unsaturated fatty acids to arrive intact in the peripheral tissues and be incorporated into cell membranes in those tissues.[59] It is also worth pointing out that the phlorotannins are self-evidently able to protect algal-derived ω3 highly unsaturated fatty acids through at least four and as many as seven trophic levels, up to and including the Inuit, over a period of many months. Finally, the lipophilic phlorotannins are so effective in preventing the oxidation of ω3 highly unsaturated fatty acids[52,53] that they are being developed for use in industrial fish processing.[54] But they also – like the general class of polyphenols – have multiple biological functions which overlap very considerably with the health benefits associated with the traditional Inuit diet.

Pluripotent polyphenols

The phlorotannins are potent anti-inflammatory agents[55–63] via mechanisms (including *inter alia* the inhibition and/or downregulation of COX-1 and -2, LIPOX-5 and -8, and the MMP group of enzymes) which complement those of the ω3 fatty acids. They demonstrate vaso-protective properties *in vitro*[64] and *in vivo*;[65] as well as additional properties that may reduce the risk of Alzheimer's[66] and cancer.[67] They also display anti-allergy, anti-coagulative, anti-hypertensive, anti-diabetic, immuno-modulatory, anti-mutagenic, anti-tumour and anti-cancer activity and can reasonably be categorised as gero-suppressants.[55–69]

In light of the above, it seems probable that many and perhaps all the health benefits associated with the tradition Inuit diet, and which were attributed to the ω3 highly unsaturated fatty acids they consumed, were at least partly due to their co-ingestion of phlorotannins.

None of this, of course, constitutes proof. There are at least two other explanations for the apparent decline in the cardio-protective properties of ω3 highly unsaturated fatty acids since DART1 and GISSI, and they are at least partly compatible. One is that the medical prevention of heart attacks has become so effective that the formerly significant protective effects of intervention with fish oils have been obliterated. The other is the effective reduction in the doses of ω3 used in the trials over time, due to steadily increasing ω 6:3 ratios in the diet and hence tissues of the general population. These have increased from 1–2:1 at the start of the 20th century[70] to 8–9:1 in the late 1930s,[71] to between 10–12:1 in the 1980s and 1990s,[72] and have reached 21:1 in the US by 2014.[c] The European diet is somewhat less processed but is following behind the US and has now arrived at 15:1.[c]

We are not making a case for the uncritical use of polyphenols, which are well known to exert anti-nutrient effects at high doses.[73] There is emerging evidence, however, that the potentially negative effects of pure ω3s are modulated by polyphenols in a way that effectively increases their therapeutic index.[74,75]

Omega 3s and due diligence

In conclusion, we believe that there is a strong case, if not a due diligence argument, for moving from purified ω3s to something that more closely approximates to the Inuit diet, combining fish oils with lipophilic polyphenols such as the phlorotannins or secoiridoids. This is, fundamentally, the same argument that has driven the evolution of infant formula, thanks to the pioneering work of scientists such as Michael Crawford, and we have just as much of a duty of care to our elders as to our infants.

Declarations

Competing interests: Mid-way through the research PC began providing consultancy services to Zinzino Ab, a company that markets *inter alia* ω3 fatty acids and polyphenols. The data on omega 6/3 ratios are derived from St Olav's Clinic at the University of Trondheim, an accredited forensic laboratory which also carries out blood lipid tests for Zinzino. SL declares no conflict of interest.

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Notes:

a. Fuel was scarce in the Far North until Western companies started to deliver bulk fuel oils in the 1980s.
b. Lipophiles such as the phlorotannins would be expected to bio-accumulate, providing increasing concentrations in the fat of different species from the base to the top of the marine pyramid. The author is currently collaborating with Norwegian scientists in a project to analyse blood and adipose tissue samples from the few Inuit elders still eating a traditional diet. The lipophile polyphenols clearly have a considerably longer half-life in the body than the hydrophilic polyphenols; their transition throughout the marine food pyramid indicates that they are efficiently stored in adipose tissues.
c. Data held at the University of Trondheim, containing over 70,000 blood samples.

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