

Fish oils in parenteral nutrition: Why could these be important for gastrointestinal oncology?

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Abstract

By the time a gastroenterology patient is moved

to parenteral nutrition, he or she is usually in poor health. All parenteral nutrition formulae contain essential nutrients, avoiding components that could cause an adverse reaction. The lipid component is often provided by a soy extract, containing all the fatty acids considered to be essential in the diet. Several trials have considered parenteral nutrition formulas with added fish oils, high in the long chain omega-3 polyunsaturated fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Given the range of biological functions associated with such compounds, especially in reducing inflammatory symptoms, this move would appear rational. However, while data from such trials are often positive, there has been variability among results. Some of this variability could be caused by environmental contaminants in the fish, and/or oxidation of the lipids because of poor storage. The situation is complicated by a recent report that fish oils may counter the effects of platinum chemotherapy. However, this effect associated with a minor component, hexadeca-4,7,10,13-tetraenoic acid. It is suggested that pure DHA and EPA would be beneficial additions to parenteral nutrition, reducing the probability of carcinogenesis and enhancing rational disease management. However, the jury is still out on fish oils more generally.

Key words: Inflammatory bowel diseases; Colorectal cancer; Fish oils; Eicosapentanoic acid; Docosahexaenoic acid

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Core tip: Parenteral nutrition formulae contain essential nutrients, in which the lipid component is often provided by a soy extract, containing essential fatty acids. Several trials have considered such formulas with added fish oils, high in the long chain omega-3 polyunsaturated fatty acids, eicosapentanoic acid (EPA) and docosahexaenoic acid (DHA). Such compounds have a range of biological functions, especially in reducing

inflammatory symptoms. However, there has been variability among results of clinical trials, possibly caused by environmental contaminants in the fish, and/or lipid oxidation. It is suggested that pure DHA and EPA, but possibly not fish oils *per se*, would be beneficial.

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PARENTERAL NUTRITION REQUIREMENTS AND FORMULATION

Both enteral and parenteral nutrition become important in the care of hospitalised patients with Inflammatory bowel diseases and many other gastrointestinal (GI) disorders^[1,2]. These formulas utilise essential nutrients, including lipids. However, there has been some controversy regarding optimal formulations, especially in regard to the nature of the most appropriate lipids^[3]. Soybean has been the basis for the most commonly used formulations, since it is a well-recognised source of the essential omega-6 polyunsaturated fatty acid (PUFA), linoleic acid, and the omega-3 PUFA, alpha-linolenic acid. It also contains the saturated fatty acids, stearic acid and palmitic acid, as well as the monounsaturated fatty acid, oleic acid^[2]. Where there seems to be some controversy is whether fish oil, which contains two long chain omega-3 PUFA, eicosapentanoic acid (EPA) and docosahexaenoic acid (DHA), adds anything of importance. Many of the controversies raised are in relation to the need for this^[4,5]. Unfortunately, however, currently available trials are underpowered to answer some of these controversies. Given the possibility that many of these GI disorders may progress to cancer^[6], the questions raised are highly relevant to GI oncology.

LIPID FORMULAE AND RISK OF CANCER INITIATION IN NORMAL SUBJECTS

Shortened telomeres have been related to significantly increased risks of cancer^[7]. Thus, there would be significant benefits in having a nutritional formula that increases the length of telomeres, or at least prevents or slows shortening. While there is no evidence that any known lipid formulas may be able to increase length, there are comparative data available for omega-3 (DHA-rich or EPA-rich) formulae, as compared with a formula containing only the omega-6 PUFA, linoleic acid. O'Callaghan *et al*^[8] supplemented elderly adults for 6 mo with each of these formulas, and compared the groups in terms of telomere length at the beginning and end of that time. They found preliminary evidence that telomere shortening could be attenuated by either of

the omega-3 PUFA-containing formulae, but not by the formula containing only the soy- derived linoleic acid.

LIPID FORMULAE AND PROGRESS OF GI SURGERY

It is difficult to compare all available studies on the effects of added fish oils to the clinical progress of GI surgery, since these are generally small, and not standard as regards to the formulae being compared in the presence or absence of fish oils^[9].

Although addition of a fish oil to an olive oil-based parenteral nutrition formula for 5 d had no effects on measures of inflammation, it appeared that GI patients showed a lower risk of infection following surgery as compared with patients nourished by the olive oil formula alone^[10].

While inflammation is necessary for responses to external challenges, there is no question but that excess inflammation is detrimental^[2,11,12], and plays an important role in the progression of GI diseases towards a cancer phenotype^[11]. A number of small studies had compared the effects of soybean oil in various combinations with medium chain triglycerides (MCT) and olive oil suggesting there may be benefits of these combinations, but larger and more systematic studies implied that this effect may not always hold^[5,10]. However, the inclusion of fish oil in combination with one of these other oils was shown to have beneficial effects on immune status and inflammatory markers in patients following major GI surgery^[2,13].

Wang *et al*^[14] compared a fish oil-enriched emulsion to an MCT/long chain triacylglycerol mix in GI surgery patients for 5 d after surgery. Clinical outcomes were comparable across the groups and there were no significant differences in standard measures of inflammation such as C-reactive protein. However, the fish oil formula led to an increase in leukotrienes B5 and B6, along with significant decreases in the pro-inflammatory cytokines, interleukin 6, tumor necrosis factor-alpha and nuclear factor-kappa B. Interleukin 6 in particular has been strongly implicated in the development of colorectal cancer^[15]. These effects all implied that inclusion of fish oil in the formula beneficially modulated inflammatory response, reducing the probability of post-surgery infection and subsequent adverse effects including CRC initiation.

LIPID FORMULAE IN COLORECTAL CANCER PATIENTS

In elderly patients after colorectal cancer surgery, Zhu *et al*^[16] found that addition of fish oil to the soybean oil-based formula again reduced pro-inflammatory cytokines, reduced infectious complications and incidence of systemic inflammatory responses, and resulted in a shorter hospital stay. In a larger trial of similar lipid mixes, this time in colorectal cancer patients

of varying ages, de Miranda Torrinhas *et al*^[17] again found improved post-operative immune responses. Thus, most of the published studies, albeit considering small numbers, suggest beneficial results from adding fish oils to the more standard parenteral nutrition formulas conventionally used.

LIPID FORMULAE IN LIVER DISEASE

A range of isolated case reports have appeared, showing significant changes in problems associated with non-alcoholic fatty liver disease, when fish oils are added to standard parenteral nutrition. For example, Crook *et al*^[18] and also Venecourt-Jackson *et al*^[19] reported on the successful treatment of parenteral nutrition-associated liver disease in individual adults using a fish oil-based formula. More generally, this area has been reviewed by several authors, including Bouzianas *et al*^[20] and Premkumar *et al*^[21]. Fish oil formulae have also benefited pediatric oncology patients who have developed liver disease^[22], and promoted high rates of resolution of cholestasis^[23].

The mechanisms of the fish oil-associated effects on liver disease are almost certainly associated with the EPA and DHA-associated shift towards anti-inflammatory proresolving lipid mediators^[24,25].

POTENTIAL PROBLEMS WITH THE USE OF FISH OILS

Despite a generally positive climate, a significant warning has been raised following evidence that addition of fish oil during a cancer chemotherapy regime containing platinum compounds may lead to cancer drug resistance^[26]. However, this effect was related to a fairly minor fish oil component, the omega-3 PUFA 16:4(n-3) (hexadeca-4,7,10,13-tetraenoic acid) that, when administered to mice, neutralized chemotherapeutic activity. Although such studies have not been done in humans to this date (and could not ethically be justified), Daenen *et al*^[26] found that, when the recommended daily amount of 10 mL of fish oil was administered to healthy volunteers, rises in plasma 16:4 (n-3) levels were observed, reaching up to 20 times the baseline levels. Herring and mackerel contained high levels of 16:4 (n-3), whereas salmon and tuna had very much lower levels. The authors concluded that, until further data become available, it may be desirable to avoid fish oil and fish containing high levels of 16:4 (n-3) on the days surrounding chemotherapy^[26].

We have previously pointed to apparently contradictory results of dietary supplementation with oily fish or with fish oils in the development and progression of inflammatory bowel diseases. The pattern which became apparent is that the nature of the results, *i.e.*, whether positive, neutral or negative, largely depended upon the source of the fish (whether polluted or not), or in the case of oils, the degree of purification and

protection against oxidation^[27]. These data are equally relevant to the case of colorectal cancer. That is, we believe that it may not only be somewhat desirable, but very important to add fish oils to parenteral nutrition therapy. However, it would also appear important that addition of the 16:4 omega-3 PUFA hexadeca-4,7,10,13-tetraenoic acid, or any possibility of formation of this product be avoided.

CONCLUSION

In summing up, there seems good evidence that the classic (usually) soy-based parenteral nutrition formulae may not provide adequate nutritional support, especially when used for patients with GI disorders. Furthermore, these formulae may themselves lead to complications, including liver disease. Fish oil-based formulae have given some extremely good results in most, but not all studies. Part of the reason for this could be environmental contaminants in the original fish source, or oxidation products because of poor storage. It would appear that a good case can be made for a strong EPA and/or DHA component, preferably as purified forms of these fatty acids, becoming an essential part of parenteral nutritional formulae. This would not only protect against the development of colorectal cancers, it would help to avoid the complications of current nutritional therapies in patients who already have the disease.

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