Commentary on the Bioavailability of Long Chain Omega-3 Fatty Acids with Emphasis on TG vs FFA Forms

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Background

Several studies have shown numerous health benefits of the long chain omega-3 fatty acids (EPA and DHA) in both humans and companion animals. The types and amounts of these omega-3 fatty acids as well as their duration of feeding are important. The amounts of both EPA and DHA in a given product are generally known and indicated on product labels. However, the issue of which type of omega-3 is more bioavailable is a question that has frequently been raised by health professionals and manufacturers. Among these types of products are triglyceride (TG), reconstituted TG (rTG), ethyl ester (EE), free fatty acid (FFA), fatty acid salts (FAsalts), and phospholipid (PL).

Most EPA and DHA are derived from fish or other marine sources in their "natural" triglyceride form, with some also present in the PL form. Various processing techniques such as molecular distillation have been used in efforts to augment their absorption and assimilation into the body. A number of studies investigating the comparative bioavailability of the various forms have been published and reviewed elsewhere[1].

To better understand bioavailabilty, some understanding of the process of digestion and absorption of dietary TG and fats containing omega-3 is needed. Briefly, during digestion in the small intestine, dietary TG containing a glycerol backbone and its component fatty acids are released in the small intestine, (facilitated by pancreatic lipase) into two fatty acids and one mono-acylglycerol species. The mono-acyl glycerol contains omega-3 fatty acid in the glycerol number two position (known as 2-MAG). Omega-3 are also in the fatty acids released. These species are next partitioned along with bile acids and other lipids (e.g. some phospholipid and fat soluble vitamins) into a "mixed micelle". This process enhances fatty acid bioavailability because 2-MAG containing omega-3 fatty acid and its glycerol backbone are directly and preferentially absorbed into the intestinal cell; then reassembled into TG. A number of studies have determined that the bioavailability and absorption of 2-MAG containing EPA/DHA is highly efficient.

Thus, having the actual glycerol backbone from fish oil TG is an important element in assuring omega-3 absorption and assimilation. It should be noted that this "2-MAG pathway" is the major route supporting TG reassembly following fat digestion in the intestinal cell.

Bioavailability Studies

Several investigations on the bioavailability of various omega-3 forms have been reported in both human and animal (i.e. rodent) studies. However, the latter tend to be highly diverse in their experimental design making it difficult to draw unified conclusions. Studies in dogs or cat were not found. One excellent peer reviewed publication describing both human and animal studies was published in 2014[1]. Another excellent summary is available online published by Holub in 2013[2]. Both reviews describe the limitations of studies performed including varying definitions of the term "bioavailability", design and methodology differences, short vs long term studies, differing amounts of fat intake among subjects, and problems in providing equal amounts of the omega-3s from different sources. Some of these studies were performed a few years ago. While still relevant, more recent investigations are needed to update current questions on the topic.

Short term studies in humans

Short term studies conducted have been postprandial in nature where a single dosage was followed by blood sampling over the course of an 8-32 hour period. Among the eight studies reviewed by Ghasemifard et al[1], all used small sample sizes. Six of the reports did not compare FFA directly with TG. The other two studies found bioavailability to be FFA > TG>EE but in one of these studies the three treatments contained different amounts of EPA and DHA of the EE form calling into question their findings. Most apparent among these short term studies overall was that TG was found to be more bioavailable than the EE form. Because it is typically necessary for omega-3 fatty acids to be fed for several weeks before health benefits can be seen, differences in postprandial blood levels may be less valuable in assessing omega 3

bioavailability. Also, because of the wide variability in the results between individual subjects and other factors, acute studies appear not to be as dependable as chronic studies in formulating conclusions with respect to bioavailability.

Long term studies in humans

Results of nine longer-term studies testing EPA and DHA bioavailability using varying experimental designs have been published ranging from two weeks to six months duration (reviewed in 1). Two of these were major long-term, well-designed omega-3 bioavailability clinical trials. Dyerberg et al[3] using a double blinded design investigated 72 subjects for a 14 day duration and found rTG > TG = FFA >EE. TG was slightly better than FFA in this study on a relative basis. Dyerberg et al considered the TG form in this study as the established standard. A six month study of 129 subjects reported better relative bioavailability of TG vs EE by approximately 15% with long-term intakes of EPA and DHA as the triglyceride form[4]. FFA were not included in this study, however. Among the other studies described, EE was typically the focus of comparisons vs either TG or krill. Comparisons between TG and FFA were less frequently seen. Given the paucity of studies directly comparing TG with FFA it is difficult to conclude that one would be better than the other. They thus appear to be roughly equivalent but with a measureable bias favoring TG based on Dyerberg et al[3]. However, a direct comparison whether in humans or companion animals under carefully controlled conditions will be is needed to best resolve this question.

Summary

The TG glycerol backbone appears to be an important and possibly essential component of fatty acid digestion including EPA and DHA. When fed in FFA form the possibility exists that other glycerol containing fats are needed to be supplied separately in order to support "mixed micelle" formation. In the case of fish oil, by comparison, glycerol from TG is already present. This difference as well those summarized below are equally important to consider when comparing the bioavailability of FFA compared to TG to assist in choosing an omega-3 supplement:

- Fish oil is a naturally occurring TG form of omega-3 containing both EPA and DHA fatty acids and glycerol. It is the omega-3 form that has been predominantly used in studies with companion animals and typically accepted as the recognized standard for comparisons.
- FFA as such may not be linked to a glycerol backbone as in the more natural TG form of fish oil.
- In the fats/oils industry vegetable oils are typically analyzed for FFA content in an effort to determine oil freshness. It is likely that intentionally generated FFA from triglycerides as an ingredient will somehow need to be additionally stabilized by various processing techniques and/or antioxidants. Differences among FFA manufacturers may exist.
- When fish oil TG are fed they are broken down into two FFA and a 2 mono-acyl glycerol species (2-MAG) with micelle formation. There is preferential absorption of 2-MAG into the intestinal cell for its further metabolism. By comparison, if only FFA are ingested, the 2-MAG species would not be present unless it were to be supplied by some other dietary component (i.e. other TG fat source?). By comparison, supplying omega-3 fatty acids as TG containing all its components (i.e. FFA and 2-MAG) assures that the appropriate amounts of each of these nutrients are available for their subsequent absorption, metabolism and health benefits.
- EPA in fish oil is more abundant in the 1-3 positions on glycerol while DHA is found in the 2 position. Thus, DHA is preferentially absorbed as 2-MAG[5] whereas EPA is absorbed from the FFA in the micelles. Although speculative, there may be differences in the amounts of each fatty acid that are absorbed possibility altering subsequent tissue enrichment and benefits between TG and FFA when fed.
- Additional studies directly comparing TG and FFA need to be performed to more definitively address their relative bioavailability in companion animals.

References

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