Fish Oil Triglycerides vs. Ethyl Esters: A comparative review of absorption, stability and safety concerns

Media exposure, scientific findings, and word of mouth have lead to a significant increase in fish oil supplementation over the past five years. The popularity of these supplements has also lead to an increased concern over product quality. The term “pharmaceutical quality” is typically associated with fish oils that are highly refined; however, the use of this term is not regulated and can be freely used by any branded fish oil product. Most experts associate pharmaceutical quality with products that comply with a fish oil monograph developed by the Council for Responsible Nutrition (CRN). The CRN Monograph established strict limits for environmental contaminants and oxidative quality parameters. Although the CRN Monograph represents an important step forward in the standardization of high quality fish oil it does not address every issue relating to quality. In particular the monograph does not differentiate between lipid classes (molecular forms). Although a product label may say “Fish Oil”, the chances are the product is not an oil at all, rather it is an alternate lipid class called a fatty acid ethyl ester (FAEE) or just EE for short. This differs in molecular structure from authentic fish oil which has a chemical structure known as a triglyceride (TG).

What are triglycerides?

The National Academy of Sciences defines fats and oils as “complex organic molecules that are formed by combining three fatty acids with one molecule of glycerol”. Triglycerides, or triacylglycerols, are the terms used to define this molecular structure combining three fatty acids (i.e. EPA and DHA) esterified (bonded) to a glycerol backbone. TGs are the natural molecular form that make up virtually all fats and oils in both animal and plants species. The omega-3 fats present in fish are almost exclusively TGs1. Because free fatty acids are rapidly oxidized the TG structure offers greater stability to the fatty acids and prevents breakdown and oxidation2.

What are ethyl esters, and how are they produced?

Fatty acid ethyl esters are a class of lipids that are derived by reacting free fatty acids with ethanol (alcohol)3. Called trans-esterification, the process involves a reaction whereby the glycerol backbone of a TG is removed and substituted with ethanol4. The resulting EE allow for the fractional distillation (concentration) of the long chain fatty acids at lower temperatures. Commonly referred to as molecular distillation in the fish oil industry this step allows for the selective concentration of the EPA and DHA fatty acids to levels greater than found naturally in fish3. The resulting EPA and DHA concentrate is typically the end product that is subsequently marketed and sold as “Fish Oil concentrate”. This situation presents several issues. Because the term fat or oil refers only to TG

the EPA and DHA ethyl ester concentrate is, by definition, no longer a fat or oil and is incorrectly marketed as fish oil. Because EEs rarely occur in nature this affects the way they are digested and absorbed in the body.

Are all fish oil concentrates ethyl esters?

The vast majority of fish oil concentrates sold globally; including those sold in North America are EPA and DHA EE concentrates. A small percentage of fish oil concentrates on the market are natural TGs. In the manufacturing of EE concentrates it is possible to convert the fatty acids back to TGs using food grade enzymes. This process, called glycerolysis, removes the ethanol molecule and re-esterifies the EPA and DHA fatty acids to a glycerol backbone. These are commonly referred to as re-esterfied or concentrated triglycerides (rTGs). The process of converting EE to TG is uncommon due to cost constraints adding 30-40 % to the end bulk oil cost. Therefore, the only rationale for omitting the glycerolysis step is cost cutting.

Absorption and metabolism of natural triglycerides vs. ethyl esters

Dietary fish oil (triglycerides) is digested in the small intestine by the emulsifying action of bile salts and the hydrolytic activity of pancreatic lipase1,5. The hydrolysis of a TG molecule produces two free fatty acids (FFA) and a monoglyceride (one fatty acid combined to glycerol)1,5. These metabolic products are then absorbed by intestinal enterocytes and reassembled again as TGs1,5. Carrier molecules called chylomicrons then transport the TGs into the lymphatic channel and finally into the blood6. The digestion of EEs is slightly different due to the lack of a glycerol backbone1. In the small intestine it is again the pancreatic lipase that hydrolyzes the fatty acids from the ethanol backbone, however; the fatty acid-ethanol bond is up to 50 times more resistant to pancreatic lipase as compared to hydrolysis of TGs7,8. The EEs that get hydrolyzed produce FFA plus ethanol. The FFA's are taken up by the enterocytes and must be reconverted to TGs to be transported in the blood1. The TG form of fish oil contains its own monoglyceride substrate; whereas EE fish oils, coupled to ethanol, do not. EE must therefore obtain a glycerol substrate from another source. Without a glycerol or monoglyceride substrate TG re-synthesis is delayed, suggesting that transport to the blood is more efficient in natural TG fish oils in comparison to EEs. Furthermore, this delay of TG re-synthesis in EE fish oils could cause an increase in free fatty acids and subsequent oxidation of those free fatty acids.

Bioavailability of triglycerides vs. ethyl ester fish oils

Numerous studies have assessed the absorption and bioavailability of EE fish oils. Most studies have measured the amount of EPA and DHA in blood plasma

after ingestion of fatty acids as either TG or EE. Although a few studies have found that the absorption rate is similar between the two types of oils, the overall evidence suggests that TG fish oils are better absorbed in comparison to EE. Natural TG fish oil results in 50 % more plasma EPA and DHA after absorption in comparison to EE oils11, TG forms of EPA and DHA were shown to be 48 % and 36 % better absorbed than EE forms12, EPA incorporation into plasma lipids was found to be considerably smaller and took longer when administered as an EE13, plasma lipid concentrations of EPA and DHA were significantly higher with daily portions of salmon in comparison to 3 capsules of EE fish oil14 and in the rat, DHA TG supplementation led to higher plasma and erythrocyte DHA content than did DHA EE15 and a higher lymphatic recovery of EPA and DHA16.

One of the causative factors for the poor bioavailability of EE is a much greater resistance to digestive enzymes. As previously mentioned, during the digestive process, pancreatic lipase enzymes hydrolyse (cleave) the oils to liberate the fatty acids and EEs are much more resistant to this enzymatic process than the natural TG form7. A recent study assessed the specificity of five lipases towards EPA and DHA in TG and EE forms. All of the investigated lipases discriminated against both EPA and DHA more in EE than in the natural TG oils. In other words, both EPA and DHA were more easily hydrolysed from a TG than from an EE. EPA and DHA hydrolysis would be further compromised in individuals who suffer from a digestive disorder, such as pancreatic insufficiency. EEs should be avoided in such populations as they would likely cause malabsorption of EPA and DHA. Review of the existing literature provides evidence which, suggests that omega-3 fatty acids in the natural form of TGs are more efficiently digested and significantly better incorporated into plasma lipids in comparison to EE forms. Recently, two clinical trials have settled the debate of which fish oil form is more bio-available in humans; the ethyl ester (EE) versus the triglyceride (TG) form. The Dyerberg et al., 2010 study was done to demonstrate the differences in absorption levels of plasma EPA+DHA following consumption of various fish oil forms including EE and TG. They noticed that with about the same grand total of EPA+DHA administered to the EE and TG group compared to the placebo group, the EE form was given the lowest assimilation as a measure of bioavailability9. The mechanism of action was simple, in that, pancreatic lipase breaks down EE to a lesser extent than TG9. Since, the omega 3 fatty acid plasma profile can significantly be elevated with the consumption of TG versus EE fish oil; then clearly TG fish oil can be more effective. In another more recent study done by Neubronner et al., 2010 a similar comparison was made utilizing a different study design. A unique method of bio-availability was used (Omega 3 index) this method looks at the omega 3 FA (EPA+DHA) incorporated into the RBC membranes10. In comparison to the plasma levels measured in the Dyerberg et al., study, this method is even more specific because it can measure EPA+DHA at the level of the tissues10. Therefore, the outcome of this study showed a statistically significant incorporation of EPA+DHA in the RBC membranes via TG over EE by over 25 percent10. Therefore, in both of the above studies the overall

bioavailability of omega 3 fatty acids with equal EPA+DHA in the form of TG showed to be more effective.

Ethyl ester fish oils are less stable, and readily oxidize

Omega-3 fatty acids in the form of EEs are much less stable than those in the natural TG form and readily oxidize. The oxidation kinetics of DHA as an EE or as a TG was assessed by measuring the concentration of oxygen found in the head space of a reaction vessel with both TG and EE forms17. The EE form of DHA was more reactive, and quickly oxidized, demonstrating that EEs are far less stable and can more readily produce harmful oxidation products17. Furthermore, the stability of phospholipid, triglyceride and EEs containing DHA has been assessed18. After a ten-week oxidation period, the EE DHA oil decayed 33 % more rapidly18.

Ethyl ester fish oil safety

During the digestive process, EEs are converted back to TGs by intestinal enterocytes1 which, results in the release of ethanol. Although the amount of ethanol released in a typical dose of fish oil is small, those with sensitivities to alcohol or those who are alcoholics should refrain from the consumption of EEs. Young children may also be more vulnerable to the toxic effects of ethanol even in small quantities. The exact amount of ethanol released from the EE fish oil is dependent on the exact profile of the fatty acids. For a typical 60 % omega-3 EE concentrate the amount of ethanol would be approximately 15 % by weight (see Figure 1). Additional concern exists regarding whether a small portion of EE is absorbed directly into the body19. Unlike TGs, the presence of EEs in the body has been found to potentiate cytotoxicity19. Several in vitro studies using purified lysosomes20, purified mitochondria19 or intact Hep G2 cells22 have provided evidence for toxicity of EEs. Studies in animals have shown that ethanol released into the liver and pancreas can result in severe organ damage23. Post mortem organ analysis has demonstrated that EEs are toxic mediators of ethanol induced cellular injury24, and have been shown to induce pancreatic injuries when infused in vivo into rats25. It is possible that efficient EE digestion in the GI tract could prevent toxicity3, but until further studies carefully examine EE oxidation, the potential for direct uptake of EEs, or EE absorption into the circulation via the stomach, EEs should be consumed with caution.

How can I determine if my fish oil is a natural triglyceride or an ethyl ester?

There is a simple, inexpensive and rapid method to determine if a fish oil supplement is in the TG or EE form by using polystyrene (Styrofoam) cups.

Method

Measure and place fish oil in a polystyrene cup. Place the cup on a plate to avoid any mess. Observe the cup after 10 minutes. If the fish oil has leaked significantly through the cup it contains EE. Due to their chemical composition, EE will actually eat straight through the polystyrene cup.

Conclusion

Fish oil supplements in the natural TG form offer numerous advantages when compared to those in the EE form: oils in a TG form are completely safe to consume, are naturally occurring, provide increased absorption, and are much more stable. Therefore, since TG fish oil can be more effectively absorbed then it can be potentially better at reaching therapeutic ranges in comparison to EE fish oil. While EEs are a source of omega-3 fatty acids, research shows that they are not as beneficial as TGs and additional research is required to fully assess potential toxicity. While some countries (e.g. Australia) have gone as far as banning the sale of EEs, other countries such as the US, Canada, and the UK allow the sale of the EE form and furthermore do not require any additionally labeling.

Short Study Descriptions

Hansen JB, Olsen JO, Wilsgard L, Lyngmo V, Svensson B. Comparative effects of prolonged intake of highly purified fish oils as ethyl ester or triglyceride on lipids, haemostasis and platelet function in normolipaemic men. Eur J Clin Nutr,47, 497-507. 31 normolipaemic non-obese men (21-47 yrs) were given 4 g highly purified omega-3 ethyl ester fatty acids, 4 g corn oil as a placebo, or 12 g n-3 triglycerides for 7 weeks. The daily intake of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) was 2.2 and 1.4 for TG, and 2.2 and 1.2 for EE. Blood samples were collected at week 1, 3 and 7. Comparison of time course incorporation of n-3 fatty acids in plasma phospholipids by repeated measures of variance did not show any difference between the TG and EE n-3 sources. Repeated measure ANOVA did however reveal a significant difference between TG and EE with respect to the incorporation of EPA into plasma cholesterol esters. Argument is made that higher amounts of omega-3 fatty acid lead to decreased differences between absorptions. Although higher doses of omega-3 fatty are not always realistic.

Beckermann B, Beneke M, Seitz I. 1990. Comparative bioavailability of eicosapentaenoic acid and docosahexaenoic acid from triglycerides, free fatty acids and ethyl esters in volunteers. Arzneimittelforschung, 40(6):700-4.
The bioavailability of EPA and DHA from triglycerides, free fatty acids and ethyl esters was investigated in 8 female volunteers in a randomized triple cross-over trial with baseline control. EPA/DHA was administered in capsules in form of triglycerides, free fatty acids and ethyl esters. The resulting EPA/DHA plasma levels were determined and evaluated. The mean relative bioavailability of EPA/DHA compared to triglycerides was 186/136 % from free fatty acids and 40/48 % from ethyl esters. Maximal plasma levels were about 50 % higher with free fatty acids and about 50 % lower with ethyl esters as compared to triglycerides. The tolerability of the free fatty acids was much worse than that of triglycerides and ethyl esters. The main side effect was eructation.

Krokan HE, Bjerve KS, Mork E. 1993. The enteral bioavailability of eicosapentaenoic acid and docosahexaenoic acid is as good from ethyl esters as from glyceryl esters in spite of lower hydrolytic rates by pancreatic lipase in vitro. Biochim Biophys Acta,1168, 59-67.
Enteral absorption by healthy male volunteers of EPA and DHA from an ethyl ester andnatural triglyceride fish oil was found to be similar after intake of equivalent doses, however; hydrolysis of natural triglyceride fish oil was more efficient. In spite of the similar serum levels of EPA and DHA obtained in vivo, in vitro hydrolysis by porcine pancreatic lipase of the ethyl ester was 3-fold slower than hydrolysis of a the triglyceride. Under similar conditions release of AA from triglyceride and ethyl ester was essentially similar and approx. 1.5-fold faster than release of EPA and DHA from ethyl esters. There are therefore differences in the rate of hydrolysis of ethyl ester and triglycerides fish oils.

el Boustani S, Colette C, Monnier L, Descomps B, Crastes de Paulet A, Mendy F. (1987). Enteral absorption in man of eicosapentaenoic acid in different chemical forms. Lipids, 10, 711-4.
After administering the equivalent of 1 g of EPA in four different chemical forms, the kinetics of EPA incorporation into plasma triglycerides were compared by gas liquid chromatography on a

capillary column following separation of the lipid fraction by thin layer chromatography. EPA incorporation into plasma triglycerides was markedly smaller and later when EPA was administered as an ethyl ester rather than as EPA free fatty acid, EPA arginine salt or 1,3-dioctanoyl-2-eicosapentaenoyl glycerol. Our results and the data in the literature are compatible with the hypothesis that the glycerol form of EPA is absorbed with minimum hydrolysis and escapes random distribution between the other positions of the glycerol molecule during the absorption process.

Lawson LD, Hughes BG. (1988). Human absorption of fish oil fatty acids as triacylglycerols, free acids, or ethyl esters. Biochem Biophys Res Commun, 52, 328-35.

As triacylglycerols, eicosapentaenoic acid (1.00 g) and docosahexaenoic acid (0.67g) were absorbed only 68 % and 57 % as well as the free acids. The ethyl esters were absorbed only 20 % and 21 % as well as the free acids. The incomplete absorption of eicosapentaenoic and docosahexaenoic acids from fish oil triacylglycerols correlates well with known in vitro pancreatic lipase activity.

Visioli F, Rise P, Barassi MC, Marangoni F, Galli C. (2003). Dietary intake of fish vs. formulations leads to higher plasma concentrations of n-3 fatty acids. Lipids, 38, 415-8. For six weeks, volunteers were given 100 g/d of salmon, or 1 or 3 capsules of ethyl ester fish oil/d. Marked increments in plasma EPA and DHA concentrations (microgram/mg total lipid) and percentages of total fatty acids were recorded at the end of treatment with either omega-3 capsules or salmon. Increments in plasma EPA and DHA concentration after salmon intake were significantly higher than after administration of capsules. The same increments would be obtained with at least two and nine-fold higher doses of EPA and DHA, respectively, if administered with capsules rather than salmon. We provide experimental evidence that natural omega-3 fatty acids from fish are more effectively incorporated into plasma lipids than when administered as capsules.

Valenzuela A, Valenzuela V, San hueza, J, Nieto S. (2005). Effect of supplementation with docosahexaenoic acid ethyl ester and sn-2 docosahexaenyl monoacylglyceride on plasma and erythrocyte fatty

acids in rats. Ann Nutr Metab. 49, 49-53.Female rats received a 40 day supplementation of either DHA ethyl ester or DHAmonoglycerate. Plasma and erythrocyte fatty acid composition were assessed by gas chromatography at day 0 and 40 of supplementation. DHA ethyl ester increased plasma and erythrocyte DHA by 15 and 11.9 %, respectively, with no modification of arachidonic acid (AA) con tent. DHA-monoglycerate supplementation increased plasma and erythrocyte DHA by 24 and 23.8 %, respectively, and reduced AA by 5.5 and 3 %, respectively. Although this data is done with animals, the authors conclude that in the rat, DHAmonoglycerate supplementation allows a higher plasma and erythrocyte DHA content than DHA-ethyl ester.

Ikeda I, Sasaki E, Yasunami H, Nomiyama S, Nakayama M, Sugano M, Imaizumi K, Yazawa K. (1995). Digestion and lymphatic transport of eicosapentaenoic and docosahexaenoic acids given in the form of triacylglycerol, free acid and ethyl ester in rats. Biochim Biophys Acta; 1259: 297-304. Lymphatic transport of EPA and DHA with trieicosapentaenoyl glycerol (TriEPA) and tridocosahexaenoyl glycerol (TriDHA) was compared with the transport of ethyl ester and free acid in rats cannulated with thoracic duct. Trioleoylglycerol (TO) served as a control. Lymphatic recovery of EPA and DHA in rats given TriEPA and TriDHA was significantly higher at the first 3 h after the administration compared to those given as free acid or ethyl ester. The 24-h recovery was comparable between triacylglycerol (TAG) and free acid, while it was significantly lower in ethyl ester. The hydrolysis rate of ethyl esters was extremely low even in 6 h incubation with lipase. Although this data is done with animals, the authors conclude that there is less lymphatic recover of EPA and DHA when they are in ethyl ester form.

Nordoy A, Barstad L, Connor WE, Hatcher L. 1991. Absorption of the n-3 eicosapentaenoic and docosahexaenoic acids as ethyl esters and triglycerides by humans. Am J Clin Nutr. 53:1185-90. Five normolipemic subjects received three test meals. 1) 40g n-3 triglycerides, 2) 28 g n-3 ethyl ester plus 12 g olive oil, 3) 28 g n-3 ethyl ester and 4) 40g olive oil. When equivalent amounts of fat were given, the increase in chylomicrons and plasma triglycerides was similar; n-3 fatty acid contents were also similar after n-3 fatty acid intake as ethyl esters or triglycerides. Ethyl esters alone were well

absorbed and produced similar n-3 fatty acid responses in plasma triglycerides and chylomicrons. At 24 h after the n-3 fatty acid containing meals, the fatty acid plasma concentration of these acids was similar. This study suggests that n-3 fatty acids given as ethyl esters or triglycerides were equally well absorbed. However, the doses of fish oil given were unrealistically high thus one should be hesitant to draw conclusions from such data.

J Dyerberg , P Madsen , JM Moller ,I Aardestrup ,EB Schmidt. Bioavailability of marine n-3 fatty acid formations. Prostaglandins Leutkot. Essent. Fatty Acids 83 (2010),137-141. Seventy- two volunteers were split into 6 groups 4 of which were double blinded and 2 of which were the EE and rTG groups. Each group was given approximately the same amount of fish oil 3.1-3.6 grams and then compared to a corn oil fed placebo group. Base line plasma cholesterol esters (CE), phospholipids (PL) and triglycerides (TG) were measured as the mean increase as a grand total of the EPA+DHA present and then taken again at the end of the two week period9. They noticed that with about the same grand total of EPA+DHA administered to the EE and rTG group compared to the placebo group, the EE form was given the lowest assimilation as a measure of bioavailability. Once adjusted for the results were 76% and 134% for the EE and rTG groups respectively.

J Neubronner , JP Schuchardt, G Kressel, M Merkel, C von Schacky and A Hahn. Enhanced increase of omega-3 index in response to long term n-3 fatty acid supplementation from triacylglycerides versus ethyl esters. Eur. J. of Clin. Nutr.(2010),1-8. The study randomized 150 subjects in one of three groups; two fish oil groups versus placebo. The two fish oil groups (EE and rTAG) had the exact amount of combined EPA+DHA per capsule and the total dose per day was 1.68grams. The two fish oil groups were compared to a corn oil placebo group and the duration of the study was 6 months. A unique method of bio-availability was used (Omega 3 index) this method looks at the omega 3 FA (EPA+DHA) incorporated into the RBC membranes. Therefore, the outcome of this study showed a statistically significant incorporation of EPA+DHA in the RBC membranes via re-esterified triacylglycerides (rTAG) over ethyl esters (EE) by more than a 25 percent.

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