What Does Science Say? Bioavailability of Triglyceride vs. Ethyl Ester Forms of Fish Oil

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Introduction

Some sellers of fish oil products make superiority claims about the TG form of fish oil, compared to the EE form. This paper reviews current science on the bioavailability of omega-3s in human health.

Background

Triglycerides are a form of dietary fat. Most fats in foods—vegetable oils, meats, dairy foods, and fish— exist in triglyceride form. Most of the fat in our blood are triglycerides and this form is the predominant form stored in adipose tissue. A triglyceride (TG) molecule is composed of three (3) fatty acids attached to a glycerol backbone by an ester bond. The fatty acids can be saturated, monounsaturated, or polyunsaturated. In fish, about 20-30% of the triglycerides are omega-3 fatty acids: EPA, DPA, or DHA.

Non-concentrated fish oils and cod liver oils are pressed from fish and from cod livers, so they are also 20-30% omega-3. These oils are in the natural triglyceride formb and are sometimes called nTG oils.

To produce fish oil supplements with meaningful doses of EPA and DHA Omega-3 per serving, omega-3s are concentrated up from the starting 20-30% omega-3 in unprocessed fish oil. Concentrated products contain fish oil in either ethyl ester (EE) form or re-esterified triglyceride (rTG) form.

> The 'EE vs TG' discussion refers only to fish oil supplements that have been concentrated and specifically refers to EE and rTG form, not the nTG form.

Consumers and health professionals like concentrated fish oil products. Higher doses of EPA and DHA are often required to achieve desired nutrition and health benefits. Concentrated fish oil products can provide double or more of the amount of EPA and DHA than regular fish oil but not at double the price. Concentrated fish oil products offer more omega-3 in fewer capsules and are often a better value.

Manufacturing concentrated fish oil: EE and rTG forms

To begin, the three types of fatty acids (saturated, monounsaturated, or polyunsaturated) in the triglyceride are liberated from glycerol and attached to an ethyl alcohol and become ethyl ester (EE) fatty acids. The production of the EE form is a necessary first step. Conversion into the EE form allows omega-3 fatty acids to be separated from the saturated and monounsaturated fatty acids without damaging the omega-3s. At this point, EE omega-3s (EPA, DHA, or DPA) can be molecularly distilled, concentrated to the desired level, delicately purified, and encapsulated, or it can be further processed into a rTG fish oil product.

To produce a rTG fish oil, the EE omega-3 fatty acids are enzymatically re-attached to a vegetable glycerol molecule by a process called re-esterification (rTG), and then distilled, concentrated, purified, and encapsulated. Note that not all of the fatty acids are re-attached as triglycerides: according to The European Pharmacopoeia, a rTG must contain at least 60% triglycerides; the rest is di-glycerides and mono-glycerides. Technology has improved; some manufacturers are now able to employ sophisticated processes to produce rTG oils that contain up to 80-90% triglycerides. This additional processing (re-esterification) adds additional cost to the final product.

Currently, no distinctions or labeling is required for natural triglycerides vs. re-esterified triglycerides, and companies generally refer to both forms as 'natural'. There are, however, distinct differences in the composition of these two TG forms. In fish and in non-concentrated fish and cod liver oils (nTG), the omega-3 fatty acids are typically, naturally bound to the glycerol molecule in the middle position (SN-2) and hence contain about 20-30% omega-3. In other words, about one out of three fatty acids attached to the glycerol molecule is omega-3 (the 20-30%). In contrast, during production of rTG fish oils, the omega-3 fatty acid is randomly attached to any position on the glycerol molecule (SN-1, 2, or 3) and the statistical probability is that more omega-3 will attach at SN-1 and/or SN-3 than at SN-2. It is unknown if any physiological differences exist due to the location of attachment of the omega-3 fatty acids to the glycerol. Though claims are made, a preliminary human study suggests that the location of attachment does not affect absorption. 1

It is often argued that the rTG form of omega-3 is natural and the EE form is not, but in reality, both EE and rTG forms of fish oil are relatively new as concentration of fish oils began in the 1980s. 2

Absorption

Under normal conditions, humans absorb 85-95% of the fat we consume. 3 Research has also shown that we absorb omega-3 from fish and fish oil capsules equally well. 4 It is the tissue levels of omega-3 that matters most. Regardless of the form (e.g., EE) or source (e.g., fish or supplements), improving tissue levels of omega-3 takes time.

Bioavailability

Bioavailability is the degree and rate at which a nutrient is absorbed or made available at the site of physiological activity. There are essentially two definitions of bioavailability:

- Short-term bioavailability measures the amount and rate at which a nutrient gets absorbed and enters the blood stream.
- Long-term bioavailability measures how much and how effectively a nutrient reaches its target tissue where it is physiologically active.

There are substantial differences between these two types of bioavailability. For example, the amount of omega-3 fats that enter the bloodstream is different from (and greater than) the amount that reaches target tissues. Measuring levels of omega-3s in the blood is relatively simple and inexpensive, but the conclusions that can be made from this information is limited because omega-3s are not active in the blood stream; omega-3s function in tissue. Blood levels of omega-3s change within hours of intake but this doesn't reflect tissue, or cellular, levels. It is the amount of omega-3 that reaches 'steady state' levels in tissues that matters. Membrane tissue levels are the best measure of omega-3. It takes 8-12 weeks to see meaningful changes in tissue levels, and it takes months of consistent consumption for tissue levels to stabilize, or reach 'steady state'. Furthermore, individual factors such as age and body weight influence how much omega-3 reaches tissue levels. For example, it takes longer for omega-3 tissue levels to change in overweight individuals, and one study measured faster changes in omega-3 tissue levels in older individuals, compared to younger adults. 5,6,7,8 There are other factors that influence absorption of omega-3 from fish oil, too.

For example, enteric coating of capsules can delay or reduce absorption and consuming fat in a meal or snack along with the omega-3 supplement will increase absorption. 9

Clinical Research Review:

Several short-term bioavailability studies have reported no difference between the EE and TG forms:

- When two doses (35% and 54%) of EPA and DHA from nTG and EE forms were compared, no difference in absorption was measured. 10
- A comparative study of meals containing omega-3 as EE or TG showed normal absorption of both EPA and DHA. 11
- It is known that absorption of omega-3 fatty acids is better when consumed with a fat-containing meal. When researchers compared absorption of EE and TG forms in male volunteers consuming a low-fat (8g) versus high-fat meal (44 grams total fat), there was a marked increase in absorption of EE form, but absorption of both TG and EE forms significantly improved. 12
- A 2-week study in healthy males reported no difference in the absorption between EE and nTG omega-3 when the equivalent amount of EPA and DHA were consumed. 13

One comparative study reported that rTG increased blood levels faster in the short-term:

- A 2-week study in healthy adults evaluated absorption of five forms of omega-3 fish oils: EE fish oil; rTG fish oil; free fatty acids; and fish body oil and cod liver oil containing nTG form. 1 Doses ranged between 3,100 – 3,600 mg EPA and DHA.
- Omega-3 blood levels increased at a faster rate with the rTG than with the EE form but the study didn't last long enough for blood levels to reach steady state. The different forms of fish oil were well absorbed and this study suggested there may be differences in the rate of absorption in the short-term but it does not show change in tissue levels over time. In addition, it's unknown if subjects consumed the supplements with fat-containing food or snacks.

Several longer-term bioavailability studies have reported similar benefits between the EE and TG forms:

- A 7-week placebo-controlled study that compared the impact of EE and rTG form (3,400 mg and 3,600 mg EPA and DHA, respectively) in healthy male subjects reported similar and beneficial influence from both forms on platelet function. 14
- A 12-week randomized, double-blind study compared the impact of 2,000 and 4,000 mg of EE and rTG omega-3 in subjects with elevated triglycerides. With both forms, plasma triglycerides were lowered and no differences in assimilation or triglyceride lowering were measured. 15
- A 6-month double-blind, placebo controlled trial compared the effect of 1,680 mg of EPA and DHA in rTG and EE forms on omega-3 levels in red blood cells (the Omega-3 Index). 8
- The omega-3 index increased significantly in both rTG and EE groups. It increased more in the rTG group, but again, the study authors noted that whether or not this difference has meaningful impact on clinical outcomes (e.g., reducing triglycerides, reducing risk of sudden cardiac death) is unknown. Faster increases in blood levels don't imply better efficacy.
- A 6-month randomized controlled trial in men with documented heart disease compared the effects of EE (7 grams) and rTG (6 grams) omega-3 versus placebo. In both omega-3 groups, plasma omega-3 levels increased significantly and mean triglyceride levels reduced significantly. 16

EE fish oils have an excellent safety profile:

The long-term safety of the EE form of omega-3 fish oil is excellent. Safety has been documented in thousands of human studies. 8,17,18

Conclusion

Based on clinical evidence, there does not appear to be meaningful differences in bioavailability between EE and rTG forms of fish oil.

The Global Organization of EPA and DHA Omega-3 **and** ***Health Canada*** **equally recognize EE, rTG and nTG forms of fish oil. These forms are extensively used throughout Europe and Japan.**

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