Examine.com Research Digest

Exclusive Sneak Peek

Issue 16, Vol 1 of 2 ◆ February 2016

Click here to purchase ERD

Table of Contents

Fish oil incorporation: where do other fats fit in?

Effects of dietary saturated and n-6 polyunsaturated fatty acids on the incorporation of long-chain n-3 polyunsaturated fatty acids into blood lipids

Introduction

The Examine.com page on fish oil cites 735 unique references, which speaks to the vast array of research investigating health effects of the two primary marine-based omega-3 fatty acids: eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA).

Much of fish oil's health effects come from its incorporation into cell membranes, where it is used during times of stress to help reduce inflammation. The cellular membrane ratio of omega-3 to omega-6 fatty acids is important because the stress response will use either one without discrimination, and the omega-6 fatty acids are more likely to promote inflammation.

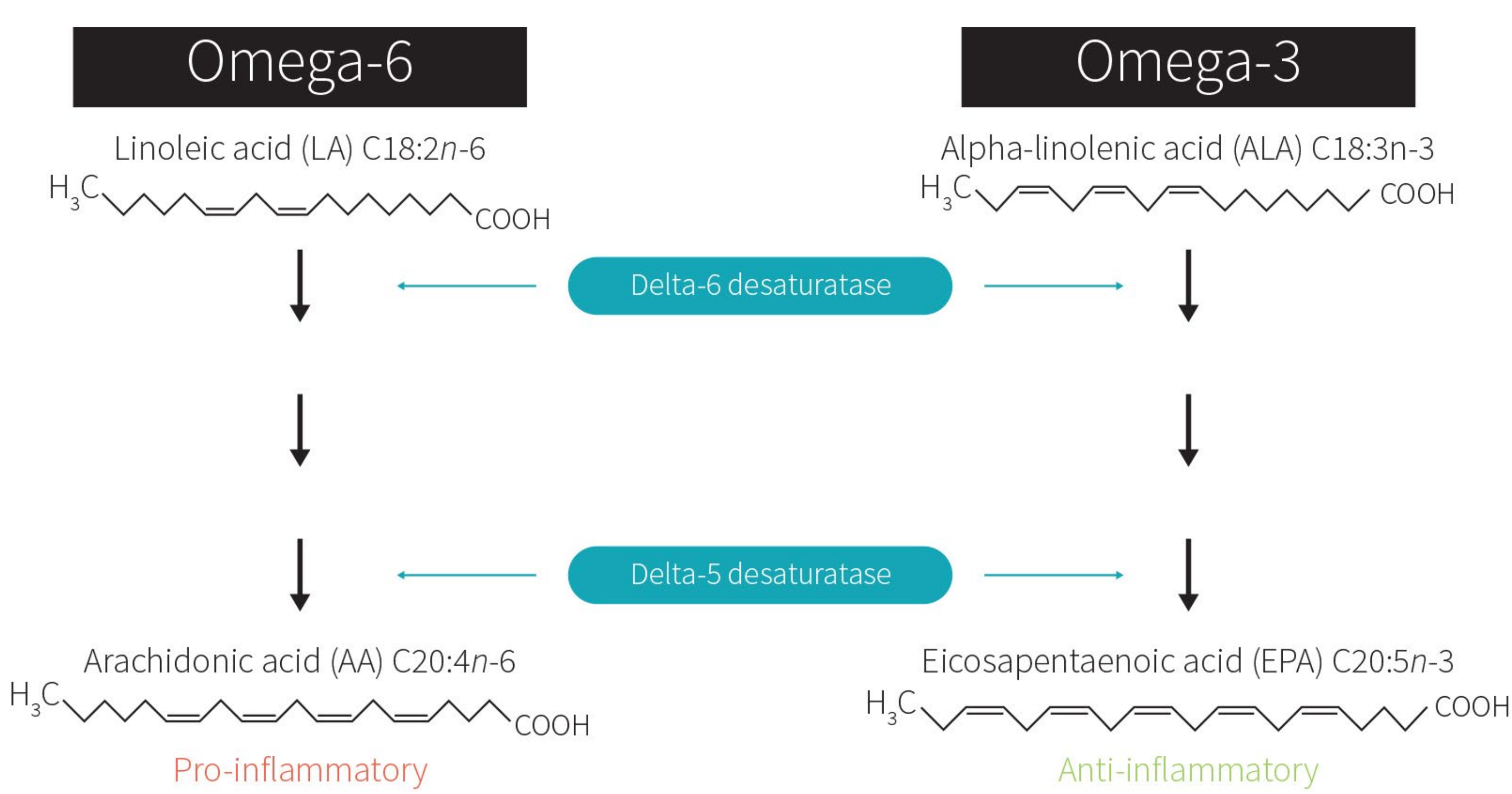
The standard Western diet has a very high omega-6 to omega-3 ratio (15:1), which is associated with many inflammatory conditions including cardiovascular disease, cancer, and autoimmune diseases. By supplementing fish oil, the omega-6 to omega-3 ratio is reduced, which can reduce inflammation and hence lower susceptibility to various chronic diseases common among industrialized societies.

Omega-3 and omega-6 fatty acids do not just compete at the cell membrane level, however, as they also share a class of enzymes that are responsible for their bioconversion. For instance, both alpha-linolenic acid (ALA, a type of omega-3) and linoleic acid (a type of omega-6) compete for desaturase enzymes (as shown in Figure 1) that are responsible for converting them into EPA and arachidonic acid, respectively.

It is possible that supplementing fish oil containing preformed EPA and DHA may circumvent the problem of competition for these enzymes. However, it has been demonstrated in rats that feeding fish oil in combination with saturated fatty acids (SFAs) increases the incorporation of EPA and DHA in cell membranes to a greater extent than feeding fish oil in combination with omega-6 fatty acids. Thus, it is important to understand how the background diet may influence the effect of fish oil supplementation in humans.

The study under review aimed to compare the degree of EPA and DHA incorporation into cell membranes and the effects on blood lipids in humans consuming a SFA-enriched diet or an omega-6-enriched diet.

Figure 1: How omega-6 and omega-3 fatty acids compete for desaturases



The benefits of fish oil may come in part through balancing the body's ratio of omega-3 to omega-6 fatty acids, which has downstream anti-inflammatory effects. Human studies have not yet investigated how fat composition in the background diet may influence the effect of fish oil supplementation. The current study aimed to fill this knowledge gap.

Who and what was studied?

This randomized controlled, parallel, dietary intervention trial involved 25 healthy, normal-weight adults (20 women) who did not regularly consume fish oil supplements or more than one fish meal per week over the past month.

All participants were provided fish oil capsules containing 100 milligrams of EPA and 500 milligrams of DHA and were instructed to consume four per day for a total daily EPA and DHA intake of 400 and 2000 milligrams, respectively. Additionally, the participants were randomized into one of two groups that increased consumption of SFAs (SFA group) or omega-6 PUFAs (omega-6 group).

The SFA group increased their consumption of SFA through the daily incorporation of 24 grams of butter and 40 grams of white chocolate (providing 30 grams of total fat and 20.9 grams of SFA) that was provided by the researchers. The omega-6 group consumed 20 grams of margarine and 42 grams of sunflower seeds (providing 30 grams of total fat and 20 grams of omega-6 PUFA). Both groups were also advised on how to use more foods and oils containing SFA or omega-6 PUFAs for cooking, and all participants were advised not to change their physical activity levels or any other aspect of their habitual diet.

Blood samples were taken to assess lipid profile and the fatty acid composition of the plasma and red blood cells (RBCs). Three-day food logs were used to measure nutrient intake. They were collected before and after the six-week intervention. Compliance was monitored by counting returned fish oil capsules and other food products provided, interviewing volunteers about their food

> "[...] the similar increases in plasma DHA content were observed despite the omega-6 group having significantly lower concentrations at baseline, indicating that the relative change was greater in this group compared to the SFA group."

consumption at the end of the trial, evaluating dietary records, and analyzing plasma fatty acid composition.

This study was conducted using a small, mostly female group of study participants who were healthy, of normal weight, and having a low baseline intake of fish oil. They all consumed four fish oil capsules a day containing 100 milligrams of EPA and 500 milligrams of DHA for six weeks, and were randomized to also eat diets either high in either saturated fat or omega-6 polyunsaturated fat. Blood lipids and fatty acid profile of red blood cell (RBC) membranes and plasma were measured.

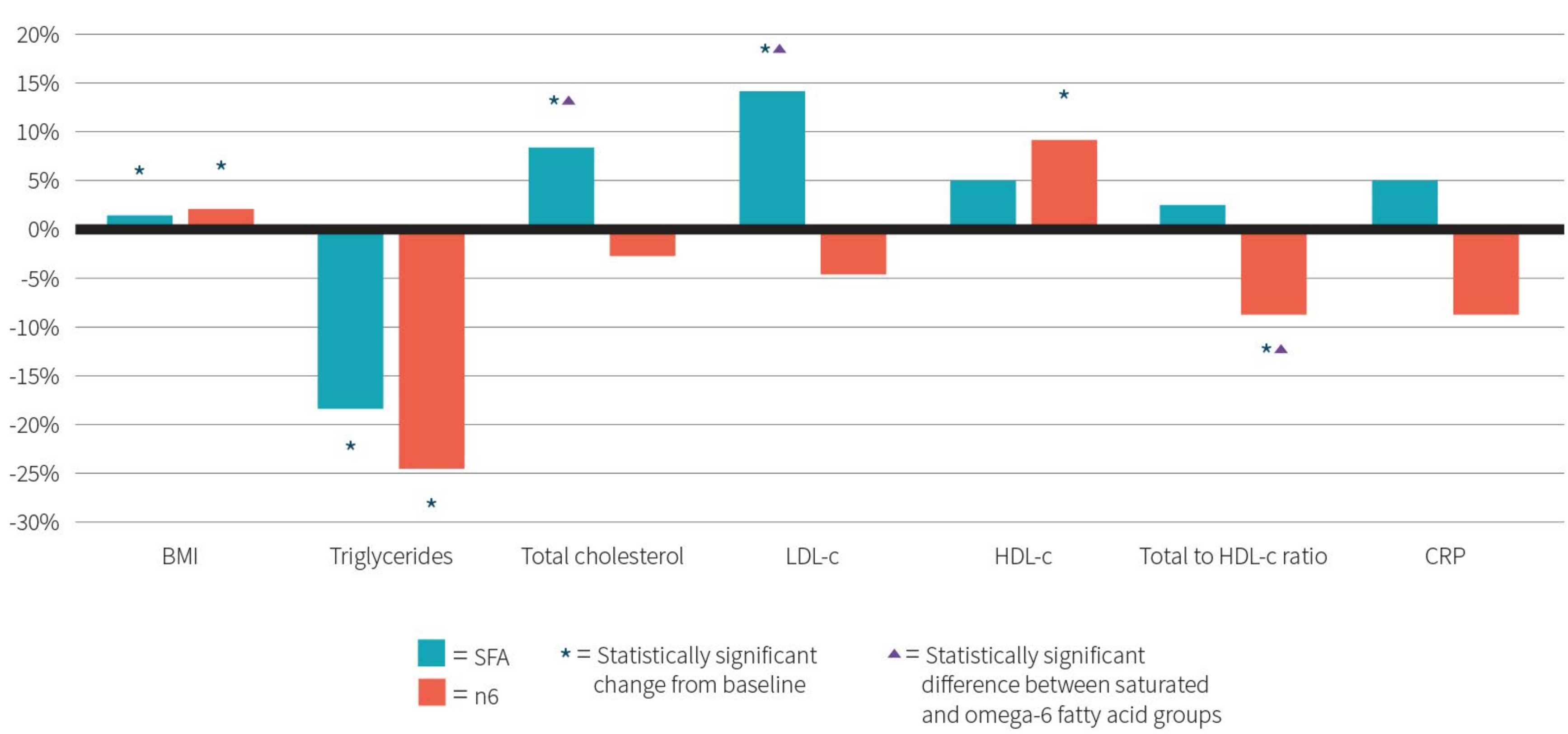
What were the findings?

Food logs revealed that the SFA group significantly increased their intake of SFA and significantly reduced their intake of linoleic acid, while the opposite occurred in the omega-6 PUFA group, leading to a significant between-group difference in SFA and linoleic acid intake at the end of the intervention. Additionally, carbohydrate and fish oil intake increased significantly in both groups without differences between one-another. Total calories, fat, and protein intake remained unchanged in both groups, despite the intervention foods providing an additional 450 kcal per day.

Increased consumption of fish oil was reflected in changes in both plasma and RBC fatty acid composition in both groups, which showed significant increases in the proportion of total fatty acids that were EPA and DHA. Although the increase in DHA was similar between groups, the SFA group showed a significantly greater increase in EPA compared to the omega-6 group in both the plasma and RBC membranes. Notably, the similar increases in plasma DHA content were observed despite the omega-6 group having significantly lower concentrations at baseline, indicating that the relative change was greater in this group compared to the SFA group.

Other study results are shown in Figure 2. Both groups experienced a significant, albeit modest, increase in BMI of 0.3-0.4 points. Both groups also significantly reduced triglycerides to a similar extent, by about 19-25%. The SFA group significantly increased total

Figure 2: Effects of supplementation of omega-3s plus dietary saturated fat or omega-6s on CRP, BMI, and blood lipids



cholesterol and LDL-c compared to baseline, while the omega-6 group did not, leading to a significant difference between groups at the end of the study. By contrast, the omega-6 group significantly increased HDL-c and significantly reduced the total cholesterol to HDL-c ratio, whereas the SFA group did not.

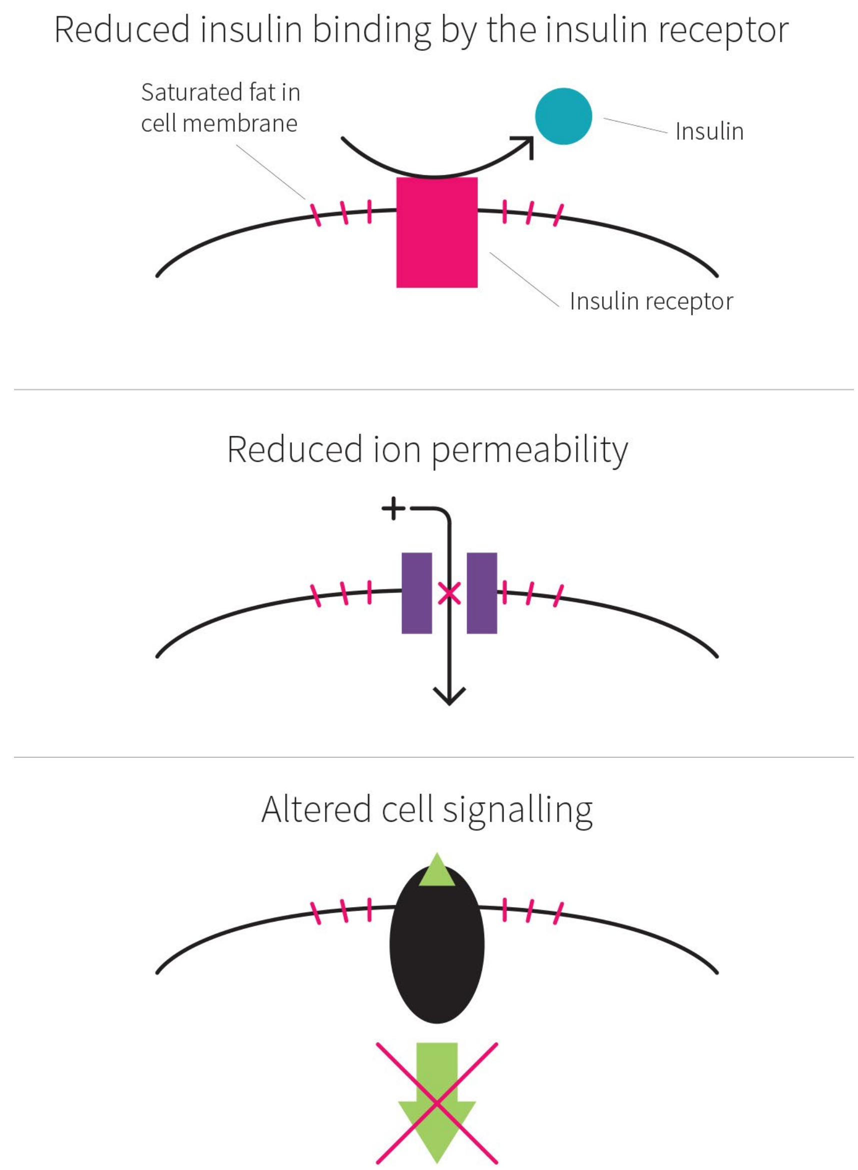
Both groups showed significant increases in plasma and red blood cell EPA and DHA, but a difference between groups was observed only for EPA, with the SFA group showing a significantly greater increase. Both groups experienced the same significant reduction in triglycerides, while changes to blood cholesterol were otherwise unfavorable for the SFA group (increased total and LDL-c) and beneficial for the omega-6 group (increased HDL-c and reduced total to HDL-c ratio).

What does the study really tell us?

Supplementing with fish oil does appear to increase EPA and DHA incorporation into plasma and red blood cells independent of the background diet. However, a greater increase in EPA concentrations associated with the SFA-enriched diet compared to the omega-6 enriched diet suggests that either the SFAs themselves promote EPA incorporation, or that the omega-6 fatty acids hinder incorporation.

SFAs are more rigid than polyunsaturated fatty acids, which is exemplified by the fact that they are solid at room temperature compared to the liquid oils rich in polyunsaturated fat. This trait appears within cell membranes as well. This is believed to be one of the reasons that a high intake of SFAs reduces insulin sensitivity (with specific mechanisms shown in Figure 3). One theoretical reason for increased incorporation of EPA might involve a balancing of membrane fluidity, for the purpose of proper cell signaling or other metabolic operations.

Figure 3: Possible mechanisms by which saturated fats in cell membranes could contribute to insulin resistance



Reference: Riccardi et al. Clin Nutr. 2004 Aug.

Alternatively, it is possible that the SFA diet allows greater conversion of dietary alpha-linolenic acid to EPA compared with the omega-6 PUFA diet, because of less competition for delta-6 and/or delta-5 desaturase enzymes that convert the shorter-chained PUFAs into their longer-chained versions. This would also explain why DHA content was similar between the groups, as conversion of ALA to EPA via the desaturase enzymes is limited to about 8% while the conversion to DHA is less than 1%.

The increased incorporation of EPA into the cell membrane has important implications for the body's immune response. Although both EPA and DHA are used to produce anti-inflammatory compounds, the exact compounds created from each differ. It has been suggested that EPA is a more potent anti-inflammatory compound in animal models, and a recent meta-analysis linked greater EPA but not DHA intake to reduced C-reactive protein (CRP) in humans. That being said, the current trial did not show improvements in CRP for the SFA group in comparison to the omega-6 group, which could theoretically have been influenced by the specific foods eaten by each group.

It's also curious that both groups had similar reductions in triglycerides even though there was more EPA incorporation in the SFA group. If triglyceride levels were in part modulated by inflammation, one would expect that greater EPA incorporation would lead to lower triglyceride level. But since there was a similar reduction in triglycerides without CRP improvements in the SFA group, the current study suggest that the triglyceride-lowering effect of fish oil is not mediated by modulation of inflammation. Rather, this effect may be owed to influences on gene expression within the liver, as discussed in the FAQ.

The observed 19-25% reduction in triglycerides is comparable to a review of 38 clinical trials involving healthy, non-obese adults that concluded supplementation with a minimum of one gram per day of EPA and/or DHA could reduce triglycerides by 8-40%. Similarly, previous research in men consuming a moderate or high linoleic acid diet demonstrated comparable reductions in triglycerides of 20-25% when supplementing with a total of 2.5 grams of EPA and DHA per day. Therefore, it does not appear that the amount of SFA or omega-6 in the diet greatly influences the triglyceride-lowering effects of fish oil.

This study has several limitations, including a lack of control groups that consumed the SFA- or omega-6 fatty acid-enriched diets without fish oil supplementation, a lack of a monounsaturated fatty acid-enriched diet to provide greater insight into how this class of fat may influence the effects of fish oil (especially in light of the favorable research surrounding the Mediterranean diet), a small sample size of predominantly healthy women, and the short study duration that may have not allowed sufficient time for some metabolic differences to manifest.

It must also be acknowledged that we are limited in drawing firm conclusions regarding the "enriched" diets because we have no idea what the participants were eating. The provided foods should have increased caloric intake by at least 450 kcal, but the dietary records showed no change in caloric intake, which raises red flags about actual dietary composition. Nonetheless, we can be confident that intake of SFA and omega-6 fatty acids increased substantially in their respective groups.

> "[...] we are limited in drawing firm conclusions regarding the "enriched" diets because we have no idea what the participants were eating."

EPA incorporation into red blood cells and plasma is increased with a diet higher in saturated fat compared to omega-6 polyunsaturated fat, possibly because of enzymatic competition between linoleic acid (omega-6) and alpha-linolenic acid (omega-3) during the synthesis of EPA. However, DHA appears to be largely unaffected. The triglyceride lowering effects of fish oil appear to be independent of the background diet's fat content.

The big picture

In ERD #3, we discussed a study that investigated how incremental changes in dietary carbohydrate intake and decreases in saturated fat intake affect the plasma fatty acid profile of overweight and obese adults. It was shown that the presence of certain fatty acids in cell membranes and blood lipids may depend more on carbohydrate than fat intake, at least under hypocaloric conditions in overweight and obese people with metabolic syndrome. The study also showed that there were marked interindividual differences in outcomes.

The health implications of the above research, as well as those of the current study, are unclear. It is well known that diet influences cell membrane composition, but what impact minor changes have on health remains a mystery. There was also no measure of other notable cardiovascular risk markers such as LDL oxidation or particle size, which is a potential direction for future research.

All that being said, the current study's big picture is that supplementing fish oil when habitual intake is low leads to favorable effects on triglycerides. The background diet will influence health as well, as shown by the differences between the SFA and omega-6 groups in blood cholesterol, but perhaps the take-home message is to ensure adequate EPA and DHA intake regardless of the rest of the diet.

Frequently asked questions

How does fish oil lower triglycerides?

The triglyceride-lowering effects of the fish oils are owed to their effect on the liver. Triglycerides are secreted from the liver, packaged up within very low density lipoproteins (VLDLs). When the fish oil concentration of VLDL is increased, there is an increased attraction for the enzyme lipoprotein lipase, which acts to remove the VLDL triglycerides from the bloodstream. Additionally, fish oils may affect gene expression in the liver, inhibiting the synthesis and secretion of VLDL, decreasing fat synthesis, and increasing fat oxidation.

What should I know?

Supplementing two grams of DHA with 400 milligrams of EPA will increase EPA and DHA content of cell membranes whether the overall diet is enriched with saturated fat or omega-6 fatty acids. However, a diet higher in omega-6 fatty acids may inhibit EPA incorporation—but not DHA—because of enzymatic competition between the omega-3 and omega-6 fatty acids. What impact this has on health remains to be determined, but it does not appear to mediate fish oil's triglyceride-lowering effect. ◆

My omega-3 intake might not have the same effect as your omega-3 intake? This important topic needs more research. Talk it over at the ERD Facebook forum.