All up in your krill

Supplementation with a blend of krill and salmon oil is associated with increased metabolic risk in overweight men

Introduction

Fish oil. By now, most of our readers have heard of it. Fish oil has been tested as a potential cure for just about everything under the sun. From treating epilepsy (covered in ERD issue #1), to preventing cognitive decline in the elderly, to reducing fatigue. The Examine.com page on fish oil currently has more than 700 citations and over 90 categories in the Human Effect Matrix, which covers each of the known effects of a supplement.

However, not as many people know about krill oil: fish oil's lesser known cousin. Both contain the omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which are the primary catalysts for many of fish oil's benefits. However, krill oil has a distinct advantage in that it may be better absorbed than fish oil. One trial has suggested that the EPA in krill oil may be taken up better depending on the type of oil. A preliminary trial has even indicated that krill oil could potentially be superior at improving cholesterol profiles over fish oil. Krill oil also contains astaxanthin, a potent antioxidant that gives salmon and krill their reddish pigmentation. Figure 1 shows a selection of health effects that astaxanthin has been researched for (albeit not combined with krill oil, and at varying doses).

And yet, research into krill oil is not terribly extensive. The study under review helps expand krill oil's evidence base by examining its use as a means to improve insulin sensitivity. Insulin sensitivity refers to how much insulin the body needs to produce in order to manage blood sugar levels. Being insulin-sensitive is a sign of metabolic health, while insulin resistance can be a warning sign of metabolic dysfunction. People with insulin resistance would need their body to pump out a lot of insulin to bring blood glucose down to a normal level. Before the publication of this study, no human trials had investigated the outcomes of krill oil supplementation on insulin sensitivity. Previous research had found omega-3 fatty acids to exert little positive or negative change on insulin sensitivity, but these studies

Figure 1: Some human effects (or lack thereof) of astaxanthin

used a number of different omega-3 sources, varying doses, assorted control oils, and had confounding variables, like restricting participant calories in addition to administering an omega-3 supplement. Complexities like these make it hard to determine the true relationship between insulin sensitivity and omega-3s.

Although the sum of evidence to date shows little change in insulin sensitivity after omega-3 supplementation, there are many confounding variables that make it hard to say if omega-3s have an effect or not. Krill oil may possess some unique properties that could give it an advantage over fish oil, since it is easily absorbed and contains astaxanthin, an antioxidant.

Who and what was studied?

This study was a double-blind, randomized, controlled, crossover human trial investigating the effects of a krill and salmon oil blend (88%/12%, respectively) on insulin sensitivity in overweight middle-aged men. In a crossover trial design, all participants receive the treatment and the placebo in a randomly assigned order. For this 24-week study, three eight-week periods were used to test the krill/salmon oil blend. In the first eight weeks, half the participants received the krill/salmon oil and the other half received canola oil. After an eight-week washout period, during which no supplements were taken, participants switched to the opposite treatment for the last eight weeks.

The 47 participants were middle-aged men (35-55 years old) who were classified as being overweight (BMI 25-30) but were otherwise healthy (e.g. did not have diabetes, high blood pressure, high cholesterol, and did not use tobacco). The researchers noted that women were excluded from participating because menstrual cycles and contraceptives can affect insulin sensitivity, which could have confounded the study results. Men who took medications that could affect insulin sensitivity were also excluded.

The two study groups received one of the following: five grams of a krill/salmon oil blend or five grams of canola oil. Both oils were tested to ensure that they had not oxidized or gone rancid. Omega-3 fats in fish and krill oils are particularly susceptible to oxidation. Once these fats oxidize, their many potential health-promoting properties are diminished. These effects are explored further in the sidebar.

Insulin sensitivity was measured on four occasions, before and after the first and last eight-week periods, using an oral-glucose-tolerance test (OGTT). To take this test, participants are brought in after an overnight

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Oxidized Fish Oil

Fish oil can go rancid and oxidize when exposed to oxygen, heat, or light. These oils are particularly susceptible to oxidation because of their very long chain polyunsaturated fatty acids. The oxidation level is measured using three values: peroxide value (PV), anisidine value (AV), and TOTOX value.

The PV is a measure of primary oxidation products (peroxides) and AV a measure of secondary oxidation (aldehydes and ketones). The TOTOX values is calculated using the formula AV + 2PV. The lower the TOTOX value, the better the oil quality will be. The Global Organization for EPA and DHA Omega-3 recommends no more than a TOTOX of 26.

Oxidation of fish oils is more common than you may suspect. One study found that almost 50% of commercial fish oils exceeded the maximum recommended TOTOX value. Evidence for the health effects of consuming oxidized fish oils is a bit mixed though. For healthy individuals, it would appear that there is a lack of obvious short-term health damage from consuming oxidized fish oil. One study showed no difference in circulating levels of oxidized LDL or inflammatory markers after seven weeks of oxidized fish oil supplementation. However, in people with high levels of cholesterol and triglycerides, consumption of highly oxidized fish oils can minimize its efficiency at improving metabolic markers like fasting glucose, total cholesterol, and triglycerides.

fast and drink a solution containing 75 grams of glucose. Five blood samples are then taken over the next two hours to measure glucose levels and insulin response. The responses are used to calculate insulin sensitivity via two methods, the Matsuda Index and HOMA-IR. These measures give us a short-term snapshot of how the body responds to ingested carbohydrate and provides an overall approximation of insulin resistance. Blood samples were also taken to assess metabolic disease risk (free fatty acids, C-reactive protein) and lipid profile (total cholesterol, HDL, LDL, triglycerides).

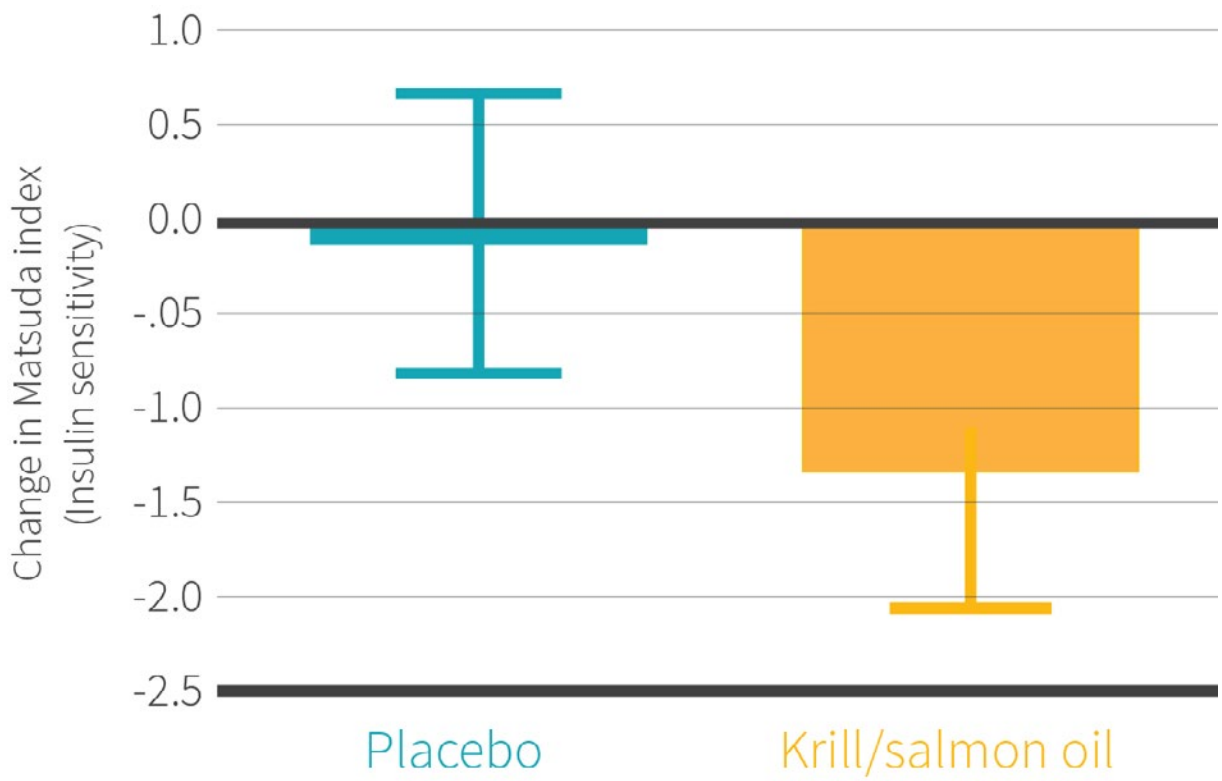
This randomized, controlled crossover trial was conducted in overweight but otherwise healthy middle-aged men. One group received a krill and salmon oil blend while the other received canola oil, which acted as the control. Participants were crossed over into the other group after an eight-week washout period. Insulin sensitivity was measured using an oral-glucose-tolerance test.

What were the findings?

The main finding is shown in Figure 2. Surprisingly, insulin sensitivity worsened, dropping 14% after krill oil supplementation, when compared to the control oil (Matsuda index - Control: 5.33, Krill Oil: 4.57). After receiving these findings, the researchers adjusted their analysis by controlling for the potential positive effects that DHA and EPA can have on insulin sensitivity. This analysis showed an even greater reduction of 27%, when compared to the control oil.

Researchers found no significant changes in the metabolic disease risk or lipid profile measurements. Results for total cholesterol, HDL, LDL, triglycerides, free fatty acids, and C-reactive protein did not significantly differ between groups. The most severe adverse event reported was a high frequency of eructation, which may sound scary, but is actually just the medical term for a belch. The authors described these belches as “fishy burps.”

Figure 2: Effect of Krill/salmon oil mixture on insulin sensitivity



The "fishy burps" experienced by participants lead to an interesting twist in the study. The majority of participants (51%) were able to guess which supplement they were taking at the end of the trial, causing the double-blinding of the treatment to be unsuccessful. One participant even admitted to cutting open his krill oil capsules to identify the contents. The researchers had been very diligent throughout the blinding process, going as far as to minimally coat the control canola oil capsules in fish oil to mimic the odor and taste of the krill oil pills. Unfortunately, their efforts were foiled by fish burps. However, there is no evidence to suggest this unintentional unblinding caused the participants to change any dietary or physical activity behaviors that could have influenced insulin sensitivity.

Krill oil supplementation caused a 27% reduction in insulin sensitivity when adjusted for the potential positive effects DHA and EPA can have on insulin sensitivity. No changes were detected in any other measures, including lipid profiles and markers of metabolic disease risk. Many participants experienced "fish burps," a common side effect of taking fish oil, which thwarted the researchers' attempts at blinding.

What does the study really tell us?

This study demonstrates that within certain subgroups, such as the overweight men examined here, krill oil may have a detrimental effect on insulin sensitivity. It is hard to determine if krill oil supplements would persistently lower insulin sensitivity when taken by overweight men, but there were certain trends and associations in participant biomarkers that could shed some light on this question. While participants supplemented with krill oil, their fasting insulin, carotid artery thickness, cholesterol, and apolipoprotein B all increased slightly.

All of these changes could potentially indicate future risk for developing metabolic syndrome. People who develop metabolic syndrome are more likely to have heart disease and to develop type 2 diabetes. These changes were only seen in a within-group analysis conducted post hoc and should be interpreted with a grain of salt. Future studies are needed to verify these findings.

The authors proposed that the unfavorable results seen in insulin sensitivity are not likely due to the omega-3

content of the krill oil, but some other chemical compound, since the reduction in insulin sensitivity got even worse when blood levels of omega-3s were taken into account. Narrowing down that compound proved to be an elusive endeavor. Since the trial used a blend of krill and salmon oil, it is hard to say which components of the two, or both, are to blame. In all likelihood, the krill oil may be the culprit, as previous fish oil studies have not shown adverse effects on insulin sensitivity. Furthermore, in one small study comparing krill and fish oil, the krill oil group saw an upward trend in fasting insulin levels, an indicator of insulin resistance. Though the researchers were not able to identify the compound responsible, they suggest it may be a protein that is not filtered out during the krill oil extraction process.

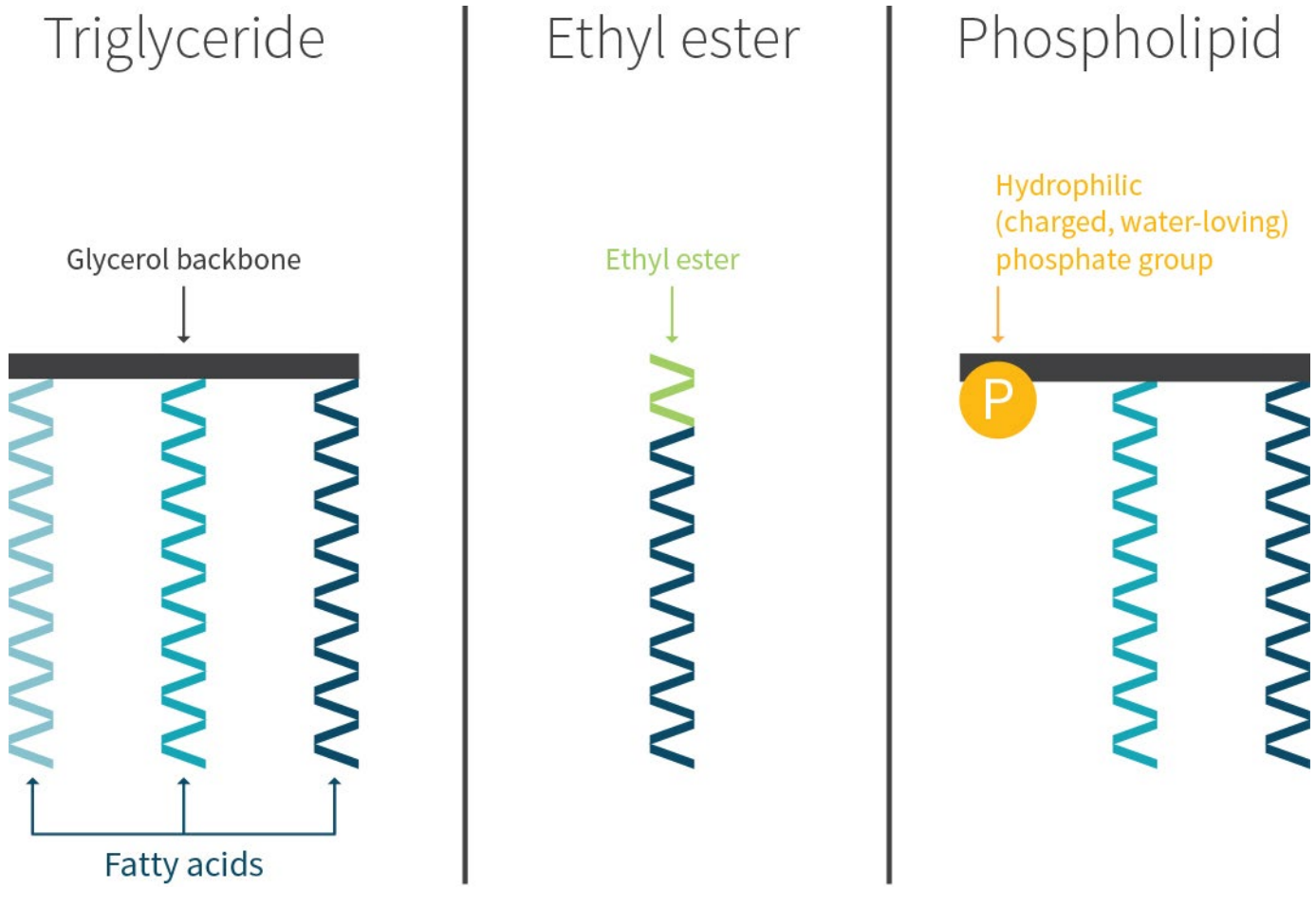
One finding of note was that the krill oil did not lower participant triglyceride levels (which are compared structurally to other fatty acids in Figure 3). Omega-3 fatty acids have been shown to be a potent treatment for decreasing serum triglycerides, but the participants in the study only experienced a tiny drop, from 105.4 to 104.5 mg/dL (1.19 to 1.18 mmol/L). This is most likely due to the fact that the participants' triglycerides were already in a healthy range at the beginning of the trial, and the dosage of omega-3 being administered was very low (230 milligrams of EPA and 154 milligrams of DHA). Trials that have shown large reductions were done on participants that already had high fasting triglycerides, who had been administered sizeable doses of EPA or DHA, usually around four grams of total fish oil. EPA tends to have a slight advantage in terms of lowering serum triglycerides.

While the krill oil did reduce insulin sensitivity, these effects may not have been brought about by its omega-3 fatty acid content. Rather, a yet to be identified protein could be the culprit. Omega-3 fats, particularly EPA, have the ability to reduce triglycerides, but only in people who have high levels and take substantial doses.

The big picture

The various studies that have looked at fish oil's effects

Figure 3: Three forms of fatty acids



on insulin sensitivity have been fairly equivocal to date. The study under review adds to the body of evidence that suggests omega-3 supplementation is unlikely to benefit insulin sensitivity. It is the first krill oil study to show significant harm to insulin sensitivity though. However, these findings have limited applicability, especially to women, as the studied participants were overweight but healthy middle-aged men of European ethnicity. Some studies have shown that some effects of omega-3s could differ between sexes.

It is not yet known if the decreases in insulin sensitivity caused by the krill oil would have long-term detrimental changes on health. Since the trial did not last long enough to give a concrete answer to this question, it would be advisable for people who fall into the "at risk" category for metabolic syndrome to seek out a fish or algal source of omega-3 oils (if they choose to supplement at all). Future research to identify which compound(s) in krill oil interfere with insulin sensitivity could lead to a better understanding of the different metabolic properties omega-3 oils can have, depending on their source. Identification of these compounds could also lead to manufacturing processes designed to remove them from the oil.

Outcomes like the krill oil-mediated insulin desensitization demonstrate why it is important to investigate krill oil and fish oil separately. As this study shows, they can have strikingly different results even when researchers are looking at the same endpoint. While fish oil is currently the more studied of the two, additional benefits of krill oil may be seen in future trials, as it contains the antioxidant astaxanthin and has may have greater EPA absorption compared to fish oil.

It is unlikely that omega-3 fatty acids can substantially improve insulin sensitivity. Due to krill oil's negative effects on insulin sensitivity, people at risk for metabolic syndrome should seek out different sources of omega-3 supplementation, such as fish or algal oil.

Frequently asked questions

I'm allergic to shellfish. Can I still take krill oil?

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The prevalence of shellfish allergy in the US has been reported at about 2% of the population.

There are trace amounts of protein in krill oil that could cause an allergic reaction. Two participants in the study under review had to withdraw due to reactions while on the krill oil supplement. Anyone with a shellfish allergy may want to seek out a non-krill oil source for their omega-3 supplementation, such as fish oil or algal oil.

Should I choose krill over fish oil since it is better absorbed?

As noted earlier, the EPA in krill oil may be absorbed better than fish oil. The current study showed that krill oil supplementation increased blood concentrations of EPA by 60% and DHA by 10%. The obvious choice may be to go with the krill oil, but at least in healthy people, there may be little difference between the effects of krill and fish oil. One study noted omega-3 blood concentrations between people taking either fish or krill were no different, nor were there any significant differences between markers of inflammation or oxidative stress. The doses used in this study may have confounded the results, as the krill group received 543 milligrams of omega-3 versus 864 milligrams of omega-3 in the fish oil group, but since blood concentrations of omega-3 were the same it indicates the krill oil may be more bioavailable. In the end, rather than fretting over which source may be minutely "better" for you, try to focus on finding a quality source for either type of oil and ensure your dosage is adequate.

What are the potential implications of unsuccessful blinding?

Blinding in clinical trials is a crucial aspect in eliminating sources of potential bias. This trial used a double-blinded protocol so neither the participants nor the trial investigators knew who was receiving which supplement. There are many benefits to this method for all blinded individuals. It makes participants more likely to comply with the full trial regimen and less likely to bias their psychical or psychological responses to the given supplement. For the researchers, blinding allows them to ensure similar and non-preferential treatment when interacting with the trial participants. Additionally, blinding helps prevent bias from creeping into the final assessments.

The blinding in this trial was unsuccessful, as the "fishy burps" experienced by many of the participants was a dead giveaway as to which supplement they were receiving. Although the participants stated they did not alter any diet or exercise habits that could affect insulin sensitivity, there remains the distinct possibility that they could have subconsciously made small, but significant changes. Participants may have slightly increased vegetable intake, daily activity, or reduced junk food, all of which can alter insulin sensitivity. Without successful blinding, the accuracy of the results of the trial can become skewed. Further replication trials would be needed to corroborate the findings.

What should I know?

Krill oil is a perfectly viable option for otherwise healthy individuals looking to supplement their diet with a quality omega-3 source. Until there is better data on the metabolic effects of krill oil, people with increased risk of type 2 diabetes or cardiovascular disease should stick with either a fish or algal source of omega-3. People with crustacean allergies should also seek out alternative sources. Additionally, omega-3 supplementation will likely not significantly improve insulin sensitivity or bring down your triglyceride levels unless they were elevated to begin with. ◆

Krill oil has gone largely unscathed during its rise as a fish oil alternative. Will this study crack its armor? Discuss krill in the ERD Facebook forum.