

Appropriate doses of omega-3 fatty acids for therapeutic results

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The November 10, 2018 issue of the *New England Journal of Medicine* contained two articles on the use of omega-3 fatty acids to treat cardiovascular conditions^{1,2}. Both studies used the same endpoint for determining cardiovascular benefits. One study (the VITAL trial) used a low-dose of omega-3 fatty acids (0.84 grams of omega-3 fatty acids) and found no cardiovascular benefits¹. The other study (the REDUCE-IT trial) used a much higher dose of omega-3 fatty acids (3.8 grams of omega-3 fatty acids) and found significant cardiovascular benefits². This difference in clinical outcomes is most likely due to dosage since the levels of omega-3 fatty acids used in the REDUCE-IT trial was 4.5 times greater than that used in VITAL trial. Furthermore, findings from the REDUCE-IT trial confirmed the 2007 JELIS Trial conducted with much larger group of patients (18,000). As in the REDUCE-IT trial, all patients in the JELIS study were also all taking statins³. The omega-3 fatty acid concentrates used in both studies are currently only approved by the FDA only to treat very high levels of triglycerides (greater than 500 mg/dL), and neither is approved for treating heart disease. In particular, one product contained a combination of EPA and DHA and the other product only contained EPA. Since the REDUCE-IT trial used the EPA-only product, this might imply that DHA has no benefits. That assumption is not supported by the data. A recent meta-analysis showed that EPA lowers LDL cholesterol levels by 0.7% and DHA raises LDL cholesterol levels by 2.6%⁴. If an individual has a high LDL cholesterol level of 130 mg/dL, this means using EPA-rich omega-3 supplements will lower their LDL cholesterol by 1 mg/dL whereas using DHA-rich omega-3 fatty acid supplements will raise their LDL cholesterol by 3.5 mg/dL⁴. These changes are clinically meaningless. Fur-

thermore, the same meta-analysis study indicated that DHA-rich omega-3 fatty acid supplements are better than EPA-rich omega-3 fatty supplements in reducing triglycerides and increasing HDL cholesterol. These differential lipid effects between EPA-rich or DHA-rich omega-3 fatty acid products essentially cancel out any differences between themselves and suggest that there are no differences between EPA and DHA in lowering total lipid levels. Thus, both EPA and DHA are beneficial in this regard. Lowering lipid levels, however, is not the reason that high-dose omega-3 fatty acids have the benefits in reducing cardiovascular events. It is well established that heart disease is an inflammatory disease^{5,6}. Much of that inflammation is mediated by pro-inflammatory proteins called cytokines. A recent Harvard study indicated that reducing one of these inflammatory cytokines (IL-1 β) using a targeted monoclonal antibody could reduce heart attacks without lowering LDL levels (7). An earlier trial in 1989 using normal subjects demonstrated that high-dose omega-3 fatty acids (5 grams per day) significantly lowered the levels of a variety of pro-inflammatory cytokines (8). The blood parameter in that trial that was most sensitive to the cytokine lowering effect of omega-3 fatty acid supplementation was the balance of arachidonic acid (AA) to eicosapentaenoic acid (EPA) (i.e. the AA/EPA ratio) in the plasma. But the therapeutic benefits of simply reducing cytokine levels can be dramatically enhanced by the simultaneous increase in a group of hormones known as resolvins. Omega-3 fatty acids can produce two groups of hormones. One group consists of primarily pro-inflammatory hormones known as eicosanoids, and the other group consists of pro-resolution hormones known as resolvins. When it comes to eicosanoids, DHA cannot produce eicosanoids

and the eicosanoids generated from EPA are actually weakly inflammatory. However, the eicosanoids generated from EPA are 10-100 times less inflammatory compared to those generated from AA. The clinical end result is that as EPA is increased at the expense of AA in the body as measured by the reduction of the AA/EPA ratio in the blood, then the intensity of any inflammatory response is significantly attenuated⁹. What might appear to be an “anti-inflammatory” effect of EPA, is actually a significant reduction of the intensity of overall inflammation. The real benefits of high-dose omega-3 fatty acids most likely come from their generation of resolvins. This is why you need both EPA and DHA as each omega-3 fatty acid generates different types of resolvins that interact with different receptors. Furthermore, you need a much higher concentration of both EPA and DHA in the blood to generate the levels of resolvins that are necessary to resolve existing inflammation¹⁰⁻¹². Thus, the real benefits of high-dose omega-3 fatty acids in treating cardiovascular disease may come primarily from their ability to increase resolvin production as well as the secondary reduction of pro-inflammatory cytokines, and with a very limited impact due to any lipid lowering properties. This would explain why the low-dose of omega-3 fatty acids used in the VITAL study generated essentially negative results¹. Unless you generate adequate levels of resolvins and simultaneously reduce cytokines by sufficiently lowering the AA/EPA ratio with high-dose omega-3 fatty acid supplementation, it is unlikely you will have significant clinical benefits. This was demonstrated in the subsequent analysis of the JELIS study when it was demonstrated that only when the AA/EPA ratio had been reduced to a level of less than 1.3 that statistically significant differences in cardiovascular events between the active and control groups become apparent¹³. It was also demonstrated in an earlier study that the level of EPA (3.8 grams per day) used in the REDUCE-IT study would lower the AA/EPA ratio to 1.2 in similar patients¹⁴. Using a lower dose of 1.9 grams of EPA per day, the AA/EPA ratio was only reduced to 2.3. Based on the clinical results of the JELIS and REDUCE-IT studies, it suggests that that the AA/EPA ratio should be reduced to less than 1.3 using high-dose omega-3 fatty acid supplementation to observe a therapeutic effect in treating cardiovascular disease. The same benefits

of high-dose omega-3 fatty acids demonstrated in the treatment of cardiovascular disease may also be applicable to the treatment other inflammatory diseases, especially auto-immune diseases such as type 1 diabetes, rheumatoid arthritis, and multiple sclerosis. Since you need both EPA and DHA for optimal resolvin benefits, I happen to believe that a 2:1 ratio of EPA and DHA should provide the greatest overall benefits to omega-3 fatty acid supplementation. The REDUCE-IT trial suggests that approximately 4 grams of EPA per day is required to get cardiovascular benefits. This suggests that to get an optimal cardiovascular result may require an additional 2 grams of DHA per day thus giving a total of 6 grams of EPA and DHA per day. For a 70 kg individual this would correspond to a dose of 86 mg of EPA and DHA per day per kg body weight. In line with that hypothesis, the recent FDA-allowed POSIDEON trial to investigate the benefits of high-dose omega-3 fatty acids and high-dose Vitamin D for the possible regeneration of beta cell activity in type 1 diabetes is using an intervention dose of 150 mg of EPA and DHA per day per kg body weight¹⁵. Case studies have suggested the possibility that such levels of omega-3 fatty acids can produce significant therapeutic benefits in early onset type 1 diabetes^{16,17}. It is virtually impossible to measure either eicosanoids or resolvins in the blood and it is relatively difficult to measure cytokines since they are intercellular signaling molecules, but you can easily measure the AA/EPA ratio using a simple finger stick method. The published data from the JELIS and REDUCE-IT trials suggests that to have maximum cardiovascular benefits, the AA/EPA ratio should be less than 1.3. This is why titrating each patient to reach a defined AA/EPA ratio should be a key experimental parameter in future clinical trials using omega-3 fatty acids if one expects to observe meaningful clinical results¹⁸. Furthermore, it is essential to measure the fatty acid composition of both the active and control groups at both the beginning and the conclusion of any trial involving the use of omega-3 fatty acid supplementation. This not only determines that significant changes are taking place in the active group, but also to account for any potential changes in the fish consumption of the control group during the trial. Such an experimental protocol was done in the JELIS study, but not in either the VITAL or REDUCE-IT trials.

CONFLICT OF INTEREST

The Author declares that he has no conflict of interests.

FINANCIAL DISCLOSURES

The author is also the President of Zone Labs, a medical food company that produces supplements and dietary food products, including purified omega-3 fatty acid concentrates.

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