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Commentary

High-dose omega-3 fatty acids and vitamin D for preservation of residual beta cell mass in type 1 diabetes

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The recent case report in the *European Review for Medical and Pharmacological Sciences* discusses the use of the combination of high-dose omega-3 fatty acids and vitamin D on the potential preservation of beta-cell mass in a recently diagnosed type 1 diabetic patient[1]. This report is suggestive for the potential of using natural nutrients at therapeutic levels to reduce inflammation caused by hyperactivity of the innate immune system as well as aiding the possible regeneration of damaged tissue by increased production of resolvins derived from omega-3 fatty acids[2].

Intriguingly, an earlier 2003 study in Norway suggested that early supplementation of the diet with cod liver oil containing vitamin D lowered the risk of developing childhood-onset diabetes by 26%[3]. The national Norwegian recommendation for infants is supplementation with 5 ml per day of cod liver oil starting seven days after birth. This volume of cod liver oil would contain 1 gram of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) and 400 IU of vitamin D. Since a typical one-year-old child weighs approximately 10 kg, this recommendation would correspond to a daily intake of a minimum of 100 mg of EPA and DHA as well as 40 IU of vitamin D per kg body weight. Thus the young patient in the published case study was consuming approximately the same levels of the EPA and DHA as well as vitamin D on a per kg body weight basis at the end of 12 months as were the Norwegian infants who seemed to be somewhat protected from developing type 1 diabetes.

Type 1 diabetes represents an immune attack on the beta cells. Activation of nuclear factor kappaB (NF-κB) is a usual suspect in this process resulting in the excess production of pro-inflammatory inflammatory cytokines including IL-1, IL-6, and TNF. In addition, pro-inflammatory eicosanoids such as the 12-hydroxyeicoetaenoic acid (12-HETE) derived by the action of the 12-lipoxygennase enzyme on arachidonic acid (AA) are also known to be toxic to the beta cells[4].

Therefore the reduction of AA to reduce the generation of pro-inflammatory eicosanoids, and the corresponding increase in omega-3 fatty acids such as EPA and DHA to reduce pro-inflammatory cytokines and increase the formation of resolvins, may offer a non-pharmacological adjuvant to moderating the consequences of early onset type 1 diabetes.

What is unique in this particular study was the use of the AA/EPA ratio as a clinical marker to titrate the levels of omega-3 fatty acids needed to stabilize the decline of C-peptide levels as well as improve beta-cell performance as indicated by an increase in the peak C-peptide secretion after stimulation by a mixed meal tolerance test.

It had been shown in 1989 that administration of 5 grams of EPA and DHA per day for 10 weeks in healthy subjects would result in a nearly 90% reduction of the AA/EPA ratio with a correspondingly significant decrease in the levels of pro-inflammatory cytokines[5]. In addition to a significant reduction of pro-inflammatory cytokines, there was also a significant reduction of the levels of AA in the plasma. Although the weight of the subjects was not stated in that paper, if it is assumed that the average weight was 70 kg, then their daily intake would have been approximately 70 mg of EPA and DHA per kg body weight or about 40% lower than the level used in the published case study[1].

The benefits of reducing the AA/EPA ratio have been confirmed in studies with fat-1 mice. Fat-1 mice are transgenic animals engineered to convert omega-6 fatty acids into omega-3 fatty acids. The result is their AA/EPA ratio is close to 1. Such

transgenic animals are protected from developing diabetes compared to wild-type controls when exposed to multiple injections of low-dose streptozotocin (STZ) that induces a direct toxic effect on beta cells[6]. In these fat-1 mice, the levels of AA are significantly lower than in the wild-type mice and the levels of EPA are significantly higher giving a dramatically lower AA/EPA ratio as well as significant attenuation of the levels of both TNF mRNA and IL-1 mRNA in the pancreas.

In this new study, the highest dose of fish oil used (113 mg of EPA and DHA per kg body weight per day) was well tolerated and without adverse events. However, the AA/EPA ratio in the subject was beginning to increase at 15 months. This may have been due to a decreased dietary compliance. It is known from studies treating children with ADHD that they can tolerate daily doses in the range of 250-325 mg of EPA and DHA per kg body weight per day and still maintain an appropriate AA/EPA ratio greater than 1[7,8]. Therefore using even higher dosages of EPA and DHA in future trials may be warranted.

High dose vitamin D has also been recently demonstrated to improve the suppressor function of T-regulatory cells in type 1 diabetics[9]. Therefore, the combination of high-dose fish oil and high-dose vitamin D appear to have synergistic anti-inflammatory properties.

Finally, it should be mentioned that high-dose polyphenols could activate AMP kinase similar to metformin to reduce insulin resistance[10].

Natural products such as omega-3 fatty acids, vitamin D, and potentially polyphenols coupled with an anti-inflammatory diet[11] will never replace the need for insulin in the management of type 1 diabetes. However, their appropriate use at therapeutic levels may reduce the levels of insulin required to manage the disease and potentially help in the preservation of residual beta cell mass.

Disclosure:

Dr. Sears is the President of Zone Labs, a medical food company.

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