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Omega-3 fatty acids and cardiovascular disease: dose and AA/EPA ratio determine the therapeutic outcome

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Two recent studies[1,2] have questioned the benefits of omega-3 fatty acid supplementation in either the treatment of cardiovascular disease or the prevention of cardiovascular disease in diabetic patients.

Cardiovascular disease can be viewed as the result of an inflammatory condition[3]. In particular, it represents an imbalance of pro-inflammatory hormones (e.g., eicosanoids) and pro-resolution hormones (e.g., resolvins). Omega-3 fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are the necessary molecular building blocks for the generation of resolvins, whereas the omega-6 fatty acid arachidonic acid (AA) is the necessary building block to generate eicosanoids. It is unrealistic to expect that the small doses of omega-3 fatty acids used in these two recent studies[1,2] were adequate to reduce a massive burden of pro-inflammatory eicosanoids derived from AA. Thus, there is no benefit if the supplemented levels of omega-3 fatty acids are not high enough to generate increased production of pro-resolution hormones needed to resolve existing inflammation, critical for the treatment of atherosclerosis[4,5]. The appropriate levels of omega-3 fatty acids required can be determined by the AA/EPA ratio in the blood[6].

It has been demonstrated that only when the daily intake of EPA and DHA exceeds 3 grams per day can resolvins be found in the blood[7,8]. The above referenced trials[1,2] focused on a substantially lower dosage. Furthermore, the amount of omega-3 fatty acid supplementation required to observe a therapeutic effect will be highly dependent on the starting AA/EPA ratio in the subjects. The lower the starting level of the AA/EPA ratio in the studied population, the lower the dose of omega-3 fatty acids that will be required to demonstrate a therapeutic effect. This is important since the largest single trial that did measure the levels of the fatty acids (and specifically the arachidonic acid (AA) to eicosapentaenoic acid (EPA) ratio) did show significant cardiovascular benefits if the AA/EPA ratio was sufficiently lowered, to approximately 0.8[9]. Subsequent post-hoc analysis of the JELIS trial demonstrated that the AA/EPA ratio is strongly associated with the improvement of cardiovascular benefits[10-12].

It is known that the average AA/EPA ratio of the American population is approximately 20[13]. Therefore, it is reasonable to assume the British population analyzed in this study would have a similar AA/EPA ratio. It has been shown that healthy American subjects required a daily dose of 5 grams/day of EPA and DHA to reduce their AA/EPA ratio from 23 to 2.5, with a corresponding reduction of proinflammatory cytokines including IL-1[14]. In addition, the recent CANTOS trial has shown that reduction of IL-1 has significant cardiovascular benefits, even in the absence of any reduction of LDL cholesterols levels[15]. It is therefore unlikely that any cardiovascular benefits could be observed in the absence of a significant lowering of the AA/EPA ratio.

In the recently reported ASCEND Study, a daily dose of 840 mg EPA and DHA long-chain omega-3 fatty acids was reported to have no effect on cardiovascular events in subjects with established diabetes[2]. The daily dose (estimated at approximately 10-12 mg EPA and DHA/kg/day) used for the diabetic patients in this study would be

insufficient to lower the AA/EPA ratio to a range that would decrease the levels of cytokines compared to the 62 mg EPA and DHA /kg/day used in an earlier study with healthy subjects[14]. This would suggest the dose used in this study was very low, and therefore one should expect minimal (if any) positive results.

It was recently reported that a dose higher than 60 mg/kg EPA and DHA was necessary to reduce the AA/EPA ratio to less than 3 in patients with type 1 diabetes[16]. With such a reduction in the AA/EPA ratio, significant improvements in glycemic control were noted, as measured by decreased insulin requirements, lowered HbA1c, and increased stimulated C-peptide production, suggesting preservation of beta cell function. This has led to the recent FDA allowance of the POSEIDON trial to study the effect of high-dose omega-3 fatty acids and high-dose Vitamin D on beta cell function[17]. It should be noted that the initial dosing level in the POSEIDON trial will be a daily dose of 150 mg EPA and DHA/kg body weight to titrate each subject to reach an AA/EPA ratio between 1.5 and 3. It should also be highlighted that this starting dose is 12 to 15 times greater than the dose used in the recent ASCEND trial - that reported negative results[2].

Future studies to determine the potential usefulness of omega-3 fatty acids in the treatment of cardiovascular disease in patients with or without diabetes should ensure that the patients have lowered their AA/EPA ratio to an appropriate range consistent with the generation of pro-resolution hormones.

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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.

Conflict of Interest:
The Authors declare that they have no conflict of interests.

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