Cardiovascular Risk and $\alpha$-Linolenic Acid
Can Costa Rica Clarify?

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Interest is increasing in the potential cardioprotective role of $\omega$-3 (n-3) fatty acids (FAs). Most of the evidence supporting this hypothesis has been derived from studies of the longer-chain members of the n-3 family, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), found in fish oils. The value of the shorter-chain cousin, $\alpha$-linolenic acid (ALA), found in certain plant oils (flaxseed, soybean, canola, walnut) has been less clear. If ALA were able to do the same “heavy lifting” that EPA and DHA do, this would be welcomed news because the capacity to produce ALA is essentially limitless, whereas there are only so many fish in the sea. Campos and colleagues report in this issue of Circulation the results of a major study conducted in Costa Rica that provided new evidence that higher ALA intakes are associated with reduced risk for nonfatal myocardial infarction.

The use of adipose tissue ALA as a marker for intake was esteemed news because the capacity to produce ALA is essentially limitless, whereas there are only so many fish in the sea. Campos and colleagues report in this issue of Circulation the results of a major study conducted in Costa Rica that provided new evidence that higher ALA intakes are associated with reduced risk for nonfatal myocardial infarction.

Three weeks after surviving a heart attack, 1819 patients provided an adipose tissue biopsy for analysis of FA stores and completed a validated food frequency questionnaire. A similar number of matching controls did the same. The authors reported a strong inverse association between myocardial infarction case status and ALA tissue levels across the range of 0.4% to 1% of total adipose tissue FAs, and this corresponded to intakes between 0.4% and 0.9% of total energy (or 1 to 2.4 g ALA per day). This is remarkably similar to the current Acceptable Macronutrient Distribution Range for ALA set by the Institute of Medicine, which is itself a reflection of the median intake in the United States. Because little difference was found in odds ratios between the 2nd and 10th deciles of intake (ie, all the risk was confined to the lowest decile) and no difference after the 5th decile for ALA tissue levels, any benefits ALA might confer seem to be achieved at quite modest intakes. This brings into question the need to recommend increased ALA intakes.

The use of adipose tissue ALA as a marker for intake was validated in this study, with these 2 showing a strong correlation across the full range of values. Nevertheless, the more graded relation between odds for myocardial infarction case status and adipose ALA than estimated ALA intake suggests (not surprisingly) that the biomarker is preferable to the dietary estimate for defining exposure. On the other hand, for EPA and DHA, adipose is a poorer biomarker of intake because the body avidly sequesters these FAs into phospholipid membranes, not triglyceride storage depots. Hence, erythrocytes (essentially pure phospholipids) are becoming the standard for assessing long-chain n-3 FA status.

The fact that, in this study, adipose ALA correlated very poorly with either adipose EPA or erythrocyte EPA is telling. It suggests that whatever benefits may be conferred by ALA, they do not appear to be mediated by the conversion of ALA to EPA as the current hypothesis holds. Furthermore, the increased odds for myocardial infarction case status were independent of EPA and DHA intake. These suggest that there may be metabolic roles for ALA per se that do not involve conversion to EPA, but such roles remain to be demonstrated.

The findings of Campos et al are somewhat at odds with those of others. In a recent meta-analysis of 6 such studies (one of which included a subset of this Costa Rican population), no significant difference was found between coronary heart disease (CHD) cases and controls in adipose ALA.8 However, the present study is, by far, the largest yet reported, and including it in the meta-analysis would likely have resulted in an overall significant case-control difference.

In exploring possible mechanisms of action for ALA, Campos et al emphasize the connection with inflammatory markers and refer primarily to studies in which significant correlations were observed. Although acknowledging in passing that not all studies support a benefit of ALA on CHD or an antiinflammatory link, they do not elaborate. But elaboration is instructive. For example, Bemelmans et al found no difference on CHD risk factors between ALA and linoleic acid, and a systematic review of 14 ALA studies examining effects on classic CHD risk factors concluded that none existed.9 A 2002 workshop convened by the Food Standards Agency in the United Kingdom to evaluate the cardioprotective potential of ALA concluded with the following: “The studies presented as part of the present workshop suggested little, if any, benefit of ALA, relative to linoleic acid, on risk factors for cardiovascular disease; the effects observed with fish-oil supplementation were not replicated by ALA supplementation.”10 More recently, Nelson et al reported that ALA at 5% energy (≈5 times the “adequate” intake) reduced adiponectin levels in humans and did not influence inflammatory markers.11 Finally, a 15-year follow-up of 1551 men in the Kuopio Heart Study found no relation between dietary ALA and CHD mortality.12 All of these negative studies do not mean that ALA has no cardioprotective properties; they do mean that ALA is not as cardioprotective as EPA and DHA.

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simply indicate that definitive demonstration of such has remained elusive.

Two randomized prospective trials are cited to support the hypothesis that increased ALA intakes reduce risk for coronary events: the Lyon Diet Heart Study (also known as the Mediterranean Diet study) and a study by Singh et al. These, unfortunately, provide a shaky foundation. The former involved a complete dietary pattern change, not just a change in ALA, and even though changes in plasma ALA correlated with benefit, this in no way indicates that the change in ALA caused the benefit. This could simply be a case of “true, true, and unrelated,” meaning that a higher ALA intake truly raised plasma ALA levels, a higher ALA intake was part of the dietary pattern that improved outcomes, but higher ALA plasma levels were unrelated mechanistically to the outcomes. The study by Singh et al is more problematic and must be discounted on the grounds of questionable validity. Our best hope of discovering a true effect of ALA on CHD risk lies with the Alpha-Omega Study. This study, in which cardiac mortality is being followed for 40 months in 4800 Dutch heart disease patients randomized to 400 mg of EPA plus DHA, 2 g of ALA, both, or neither (NCT00139464), will be the first to prospectively test whether ALA can reduce risk for clinical end points. This study is expected to be completed in late 2009.

ALA may yet prove to be a practical substitute for EPA and DHA, particularly in individuals who will not or cannot consume the marine n-3 FAs. Although the Campos study is clearly suggestive, the jury is still out until randomized trials shed more light on who can do the heavy lifting for whom.

Disclosures

Dr Harris reports having received research grants from Reliant and Monsanto, having served on the speakers’ bureau of Reliant (GlaxoSmithKline), and having served on a scientific advisory board for Monsanto Co and Reliant (GlaxoSmithKline).

References


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