

Alpha-Linolenic Acid A Gift From the Land?

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Although the fish-derived, long-chain omega-3 fatty acids (n-3 FA) may be considered “gifts from the sea” for cardiovascular health, the role of the land (or plant)-based n-3 FA α -linolenic acid (ALA) has been less clear. ALA is the 18-carbon, 3-double bond (C18:3n-3) precursor to eicosapentaenoic acid (EPA; C20:5n-3) and docosahexaenoic acid (DHA; C22:6n-3), the latter 2 being the predominant n-3 FA in fish oils. ALA is found in certain plant oils, most notably flaxseed oil (where it constitutes \approx 50% of total FA) and in canola oil (\approx 9%), unhydrogenated soybean (salad dressing) oil (\approx 7%), hydrogenated soybean oil (\approx 3%), and olive oil (\approx 1%). According to National Health and Nutrition Examination Survey (NHANES) III data, consumption in the United States currently averages \approx 1.3 g/d.

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Could ALA substitute for EPA+DHA to reduce risk for coronary heart disease (CHD) mortality? This question presumes that ALA can be bioconverted to the longer-chain n-3 FA, but the extent to which this occurs is unclear. Depending on the method used, estimates for the conversion to EPA run from 0.2% to 7% to 10%.¹ Further conversion to DHA is reported to be \approx 0.05% in men and 10% in women. Ultimately, bioequivalence will need to be demonstrated in randomized controlled trials (RCTs), not in metabolic studies.

The latest epidemiological contribution to the ALA story is reported in this issue of *Circulation*. Djousse et al² continue to mine the fertile database of the National Heart, Lung, and Blood Institute's Family Heart Study (FHS) to explore the relationships between nutrition and CHD. In this study, they examined the association between coronary artery calcification and the estimated intake of linolenic acid (LNA) obtained in 2004 subjects \approx 7 years earlier. (LNA includes two 18-carbon, 3-double bond FA: α - and γ -linolenic acid. The latter is an n-6 FA and a minor dietary component. Hence, LNA in this study is essentially equivalent to ALA.) Intakes of LNA were estimated in the mid-1990s from the semiquantitative food frequency questionnaire developed by Willett et al. The Djousse group found a significant inverse relationship

between the intake (in grams per day) of LNA at baseline and subsequent coronary artery calcification. In their most extensive multivariate model, Djousse et al found a relatively graded 65% reduction in odds ratios for calcified plaque from the lowest quintile of intake to the highest (*P* for trend $<$ 0.0001). These data support the hypothesis that LNA has antiatherosclerotic properties.

These findings are consistent with past studies from the same cohort showing beneficial relationships between LNA intake and prevalent coronary artery disease, carotid disease, and hypertension and serum triglycerides. LNA intakes (assessed with essentially the same tool) were inversely related to risk for fatal CHD in the Nurses Health Study. In a recent study, LNA was associated with reduced CHD risk, but only in subjects consuming $<$ 100 mg/day of EPA+DHA, and not in those consuming more.³ Confirmation of an LNA benefit from other prospective cohorts has been lacking, however.³⁻⁵

Epidemiology Versus Randomized Trials

Lest we too quickly forget our recent experiences with vitamin E and hormone replacement therapy, cause and effect cannot be established by epidemiology. Positive results from RCTs are absolutely essential before we can confirm a role for LNA in heart health.

Four RCTs of potential relevance to this question have been conducted; unfortunately, none was conclusive vis-à-vis LNA and CHD risk. Secondary-prevention RCTs have been reported by Singh et al⁶ and de Lorgeril et al⁷ and both are problematic. In the former, 360 patients admitted to the hospital in Moradabad, India, with a suspected myocardial infarction were randomized to placebo, fish oil (6 capsules providing 1.8 g/d EPA+DHA), or mustard oil (20 mL providing 2.9 g of ALA). They were observed for cardiac events for 1 year. The study was small, obviously was not double-blinded, and the report is internally conflicted (eg, ALA did and did not significantly lower risk) and plagued by errors in addition. What is more, the 1-year death rates were incredibly high ($>$ 35%), especially considering that these patients were only suspected of having had a heart attack at admission. By comparison, in the Italian GISSI (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico) Prevenzione study,⁸ total cardiac event rates were 1.4%/y in the usual-care group, and all of the patients in that study had documented myocardial infarctions. In the Lyon Diet Heart Study described below, the rate was \approx 4%. Thus, the report by Singh and associates is uninformative.

Although it is a much better study, the Mediterranean (Lyon) Diet Heart Study⁷ likewise cannot be used to conclude that ALA is cardioprotective. The intake levels of at least 8 types of foods (breads, fruits, vegetables, legumes, “deli” and

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regular meats, butter, cream, and margarine) were significantly altered in the intervention group. This group also received a special margarine providing ≈ 1 additional gram of ALA per day. The 50% reduction in CHD risk observed during the 3 years of the study, although impressive, cannot be attributed to any one dietary factor, including ALA. The same is true of a second study from Singh et al, in which multiple dietary components were altered simultaneously.⁹

The only primary prevention study with ALA was reported by Natvig et al.¹⁰ It used the best experimental design of all 3 studies: It had a large sample size ($n=13\,578$), was placebo controlled, and involved only 1 variable. In it, 50- to 59-year-old men were randomized to 10 g of linseed (flaxseed) oil providing 5.5 g/d of ALA or to a sunflower seed oil placebo for 1 year. There was no difference in any clinical cardiovascular end point between groups. This study is also difficult to interpret, however, owing to the short follow-up and the low death rate (0.4%). Perhaps more important is the fact that Norwegian men in the mid-1960s consumed relatively large amounts of EPA and DHA from cod liver oil, fish, and whale meat. Thus, the additional ALA may have been superfluous (as suggested by the findings of Mozaffarian et al³). We are left with tantalizing suggestions from epidemiological investigations for an LNA benefit but no properly controlled RCTs to provide a definitive answer to the question.

LNA and Plaque Burden

How does the latest contribution from the FHS advance the field? Finding that higher intakes of LNA are associated with decreased plaque burden is an important mechanistic advance, but questions remain.

First, the investigators apparently did not take into account the intake of either saturated or *trans* FA in their models. Increased intakes of each could enhance the risk of atherosclerosis and CHD. The situation with *trans* FA is especially worrisome. In the early 1990s (when the FHS dietary surveys were conducted), saturated FA were a bad player in everybody's book and efforts were under way to reduce intake. Neither the food industry nor the public was particularly concerned about the health effects of *trans* FA, however, and thus agitation to reduce their intake was embryonic at best. It was not until the mid-1990s that studies began to appear documenting the adverse effects of *trans* FA on CHD risk factors¹¹ and events.¹² When soybean oil (the most common vegetable oil consumed in the United States) is partially hydrogenated, the result is an increase in *trans* FA and a decrease in LNA. Thus, it is not inconceivable that higher intakes of LNA in the FHS study may have been a surrogate for lower intakes of *trans* FA, and the higher coronary calcium scores could have resulted not from decreased LNA but from increased *trans* FA.

Second, although they reported that the estimated intake of EPA and DHA from fish correlated positively with LNA intake, the FHS investigators did not include long-chain n-3 FA in the multivariate model. In addition, the authors expressed LNA intake by quintiles in grams per day. Had they corrected these for the reported energy intake, the mean LNA intake across the quintiles would have been (as a percentage of energy): 0.31%, 0.34%, 0.37%, 0.39%, and

0.45%, respectively. This nearly flat distribution casts some doubt on the meaning of the results as reported. Finally, the Adequate Intake for ALA from the Institute of Medicine report is 0.6% to 1.2% of energy. On the basis of these numbers, virtually the entire FHS cohort was consuming less than adequate amounts of LNA.

The authors note no relationship between LNA intakes and the n-6/n-3 ratio (because linoleic acid intakes rose in concert across LNA quintiles), but they do not make it clear which FA actually are included in this ratio. All ratios are difficult to interpret (is it the numerator, the denominator, or both that are relevant?), but the n-6/n-3 ratio is particularly problematic because both the numerator and the denominator include undefined proportions of FA with vastly different physiological effects. The n-6 FA include linoleic and arachidonic acids, and the n-3 include LNA, EPA, and DHA. Far more informative are intakes (or, even better, tissue levels) of individual FA, not classes.

Mechanistic Musings Must Mind Masses

Several potential mechanisms by which ALA may exert antiatherogenic actions such as via lower levels of inflammatory markers¹³ and adhesion molecules¹⁴ have been noted. The intakes of ALA used in the referenced studies, however, varied from 8 to 14 g/d, markedly higher than the mean intake of even the highest quintile in the FHS of 1.25 g/d. In other studies, neither 3.7 nor 15.4 g/d of ALA altered lipids or hemostatic factors as compared with a diet containing ≈ 1.1 g/d ALA.¹⁵ Controlled clinical trials examining the effects of even higher intakes of ALA on blood pressure¹⁶ and serum lipids¹⁷ would not support these as mechanistic probabilities. Accordingly, it would be premature to ascribe the putative beneficial effect of ALA on coronary calcium burden to reductions in any of these risk factors without direct evidence that LNA intakes within the observed range altered them.

Balancing Benefit With Risk

No discussion of the potential health benefits of ALA can ignore the growing—and puzzling—evidence for a positive association between ALA (intakes or tissue levels) and prostate cancer. Brouwer and colleagues conducted simultaneous meta-analyses of the epidemiological findings that associated ALA with cardiovascular disease and prostate cancer.¹⁸ They found that although the combined relative risk from 5 studies for fatal CHD was 0.79 for ALA, this was not statistically significant (95% CI, 0.60 to 1.04). According to data from 10 studies, however, the combined relative risk for prostate cancer was 1.62 (95% CI, 1.11 to 2.37) for higher ALA intakes. These data, although enigmatic at present, should give us pause. Further studies are needed to clarify the balance of risk and benefit associated with increased ALA intakes.

In summary, the epidemiological case for a cardioprotective effect of ALA has undoubtedly grown stronger with the contribution of Djousse et al.² Given the essentially inexhaustible supply of ALA obtainable from plant sources (versus the more limited availability of EPA+DHA from marine sources), the demonstration of a beneficial effect of increased ALA intakes could be translated readily into

healthier foods and have a tremendous impact on CHD risk. That demonstration will require properly sized RCTs with clinically relevant cardiac end points, not epidemiological or metabolic studies. n-3 FA are a welcome addition to the nutritional recommendations for CHD prevention,¹⁹ but we cannot yet conflate the shorter-chain interloper with the longer-chain “gifts from the sea.”

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