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n−3 Fatty acids and health: DaVinci's code[1,2]

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> Learning acquired in youth arrests the evil of old age; and if you understand that old age has wisdom for its food, you will so conduct yourself in youth that your old age will not lack for nourishment.
>
> —*Leonardo DaVinci*

DaVinci admonishes the young to feed on the wisdom of the old. In this issue of the Journal, 3 studies regarding the role of n−3 fatty acids (FAs)—eicosapentaenoic acid (EPA) and/or docosahexaenoic acid (DHA)—in geriatric populations are published. They nourish us well. Two are prospective cohort studies based on n−3 FA biomarkers (as opposed to dietary intake estimates), and the third is a randomized controlled, dose-response study. Attesting to the pleiotrophic effects of the n−3 FAs, the endpoints in these studies ran the gamut from all-cause mortality and cognitive decline in the former 2 studies to mood and mental health in the latter study. In short, the story they tell is this: low in vivo concentrations of EPA and/or DHA predict an increased risk of death in frail, hospitalized octogenarians from Norway and an accelerated cognitive decline in free-living septuagenarians from France. Hence, the ability of markers of n−3 FA biostatus continue to provide potentially relevant prognostic information for clinically important endpoints. On the other hand, intervention with EPA+DHA in the healthy elderly had no effect on mental well-being. Together, these findings suggest that dietary habits that include higher versus lower intakes of long-chain n−3 FAs may bring certain health benefits that short-term supplementation cannot provide. Supplementation can, of course, affect other factors (eg, serum triglyceride concentrations, susceptibility to arrhythmic events, and platelet aggregation (1), all with potential clinical relevance.

COGNITIVE DECLINE?

Adding to a growing literature that suggests that higher tissue concentrations of EPA and DHA are associated with slower mental decline is the report from Samieri et al (2) These investigators have expanded on their previous Tri-City study (that used dietary intake estimates (3) by measuring plasma FA composition to determine the relations between baseline n−3 FA content and the 4 y incidence of dementia. They found that the biomarker approach was a more sensitive probe of FA-dementia relations than were estimated dietary intakes. Here, the n−6:n−3 ratio and the AA:DHA ratio were both different between cases and controls. Thankfully, these investigators provided sufficient data to allow us to determine whether the n−6 FAs were elevated, the n−3 FAs were depressed, or both. Here, n−6 FAs differed not at all between cases and controls; in fact, arachidonic acid (AA, the usual villain because of its status as the precursor for proinflammatory mediators) was, if anything, a bit lower (≈4%), not higher, in those at risk of dementia. The actual problem (as usual; 4) was a statistically significant decreased concentration of n−3 FAs: EPA by 19% and DHA by 9%. Without publishing the individual FA values making up the ratio, we would not have known that the problem resided with the denominator, and not with the numerator, and hence we are at least potentially able to focus on the problem at hand, ie, decreased n−3 FA concentrations. Shortcomings of the n−6:n−3 ratio have been reviewed previously (5).

On finding decreased concentrations of n−3 FAs in the impaired, one is tempted to conclude that all we need to do is increase the EPA and/or DHA intake to alter the outcome, but clearly we cannot know from a case control study whether this is true. Only prospective trials can address this question, and, at least to date, such trials have been less than consistent, as noted by the authors. The standard conclusion follows: more studies are needed. Thankfully, several are currently underway (**Table 1**).

MOOD?

Studies of the potential benefits of n−3 FAs on mental health (as opposed to cognition), have been more common. Buoyed by the findings of investigators such as Fontani et al (6), who reported that n−3 FA supplementation improved mood indicators in 33 subjects in their mid-30s in only 35 d, a Dutch team undertook a much larger study. Enrolling 302 considerably older individuals (mean age: 70 y), van de Rest et al (7) tested the effects of 2 nutritionally relevant doses of EPA+DHA (0.4 and 1.8 g/d) on a variety of mental state metrics over a 6-mo period. These investigators found no benefit of supplementation, even in exploratory analyses in those at the higher range of depression scales. Although one can always suggest that higher doses may have been more effective, it is more likely that what is done is done; at 70 y of age, supplementation is simply unable to materially alter emotion or mentation.

DELAYED PASSING OF THE FRAIL?

The only noncognitive study in this trio involved the relations between serum FA concentrations and the risk of death from any

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TABLE 1
Randomized controlled trials of n−3 fatty acids and cognitive decline yet to be reported from clinicaltrials.com[1]

Topic	Location	Intervention	Duration	Progress	*n*	Identification no.
Fish oil and dementia	Taiwan	1.8 g EPA+DHA	24 wk	Completed (2005)	46	NCT00628017
DHA to slow progression of Alzheimer disease	USA	2.1 g DHA	18 mo	In follow-up	400	NCT00440050
PS n−3 fatty acids and memory impairment	Israel	300 mg PS n−3	15 wk	In follow-up	157	NCT00437983

[1] PS, phosphatidyl serine.

cause in frail, elderly patients (mean age; 82 y) admitted to a hospital in Trondheim, Norway. Lindberg et al (8) found that those patients with plasma phospholipid EPA concentrations in the lowest quartile were, in analyses adjusted for 11 relevant covariates, ≈40% more likely to die during the 3-y follow up period than are those in the upper 3 quartiles. DHA was unrelated to outcomes, as were the major n−6 fatty acids linoleic acid and AA. The authors concluded that only those in the at-risk quartile might have benefited from n−3 FA supplementation. Clearly, this is a speculative extrapolation; nevertheless, it is fair to say that higher tissue n−3 FA (at least EPA) concentrations appeared to be protective. Because the study population was Norwegians, who typically consume ≈1 g long-chain n−3 fatty acids/d (9), we can assume that those in the lowest quartile might be in the upper quartile in the United States, where the n−3 FA intake is much lower. Although no specific mechanism of action was identified, a generalized health benefit arising from a prolonged dietary intake of oily fish (the presumed source of the plasma EPA) would surprise no one familiar with the n−3 FA literature.

The 3 studies conducted in elderly subjects discussed above underscore the potential importance of maintaining high dietary n−3 FA intakes throughout life.

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