Achieving optimal n–3 fatty acid status: the vegetarian’s challenge . . . or not1–3

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ABSTRACT
The long chain n–3 (omega-3) fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), although originally synthesized by microorganisms in the oceans, are primarily obtained from the consumption of fish. Vegetarians, by definition, do not eat fish and thus consume virtually no EPA and DHA. Because conversion of the plant-derived n–3 fatty acid α-linolenic acid (ALA) to EPA and DHA is very low, n–3 tissue concentrations in vegetarians are lower than in omnivores. This review asks 2 questions: what is the evidence that increased n–3 concentrations reduce the risk of cardiovascular disease in vegetarians, and, if it does, how can vegetarians increase their blood and tissue concentrations of these animal-derived fatty acids? At present, both cardiovascular risk markers and cardiovascular events appear to be significantly reduced in vegetarians compared with those in omnivores. If so, and in the absence of data to show that risk in vegetarians could be even lower with higher n–3 concentrations, then the second question becomes moot. However, the absence of evidence is not evidence of absence; therefore, at our present state of knowledge, increasing n–3 concentrations is not an unreasonable goal for vegetarians. This can be accomplished by a variety of approaches, including increased intakes of ALA, consumption of stearidonic acid–enriched soybean oil (if and when it comes to the market), and the use of supplements containing EPA, DHA, or both derived from nonanimal sources (microalgae, biotech yeast, and, in the future, biotech plant oils). Am J Clin Nutr 2014;100(suppl):449S–52S.

INTRODUCTION
Others in this supplement issue have considered the topic of vegetarians and risk of cardiovascular disease in depth (1, 2). In brief, the data are quite clear that vegetarians of all kinds (vegan, lactoovo, fish-eating) are at lower risk of cardiovascular disease than their omnivorous counterparts (3). Vegetarian diets are associated with fewer coronary artery disease (CAD)4 risk factors, including serum lipids (4), blood pressure (5), and markers of subclinical atherosclerosis (6). A meta-analysis of 7 cohort studies with 124,706 participants followed for 10–23 y reported significant reductions in risk of death from ischemic heart disease (by 29%) and in risk of cancer (by 18%) in vegetarians compared with nonvegetarians with nonsignificant trends toward benefit for mortality from all causes and circulatory and cerebrovascular diseases (7). The European Prospective Investigation into Cancer and Nutrition–Oxford study examined mortality in British vegetarians and found the same amount of protection from heart disease as seen in the meta-analysis (8). Although the provision of increased amounts of α-linolenic acid (ALA) in the Alpha Omega Study did show some evidence for reduced risk of CAD events (9, 10), this study did not test a vegetarian compared with omnivorous dietary pattern, and thus it does not materially inform this review.

At the 2009 Symposium on Vegetarian Nutrition, Mangat (11) concluded that we lack convincing evidence that individuals who follow vegetarian diets would derive additional cardiovascular benefit from increased intakes (or blood concentrations) of EPA and DHA. The situation has not changed materially in 2013. No studies to date have specifically examined the associations between n–3 fatty acid intakes and/or biomarkers and the risk of CAD in a vegetarian population.

THE OMEGA-3 INDEX
In 2004, the Omega-3 Index was proposed as a new marker of risk of death from heart disease (12). The EPA+DHA content (expressed as a percentage of total fatty acids) of red blood cell (RBC) membranes has been validated as a biomarker of tissue n–3 fatty acid status (13) and reflects longer-term n–3 fatty acid status much as glycated hemoglobin does for glucose. The Omega-3 Index has been shown to be an independent risk predictor for cardiac disease (14–18), cellular aging (19), and cognitive dysfunction (20, 21). A low Omega-3 Index is also a marker for increased inflammatory status (22). Although an Omega-3 Index >8% has been proposed as optimal for cardioprotection (16, 23), the average in the United States is ~4–5% (24), with only ~10% of individuals having an index of >8%. The average Omega-3 Index in Japan, a country with one of the highest fish intakes and lowest rates of CAD is 9–11% (25, 26).

VEGETARIANS COMPARED WITH OMNIVORES AND THE OMEGA-3 INDEX
As expected, n–3 fatty acid intakes and blood concentrations are lower in vegetarians than in meat eaters (27). In a small study

4 Abbreviations used: ALA, α-linolenic acid; CAD, coronary artery disease; RBC, red blood cell; SDA, stearidonic acid.

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in Dutch vegans, the Omega-3 Index was half that in omnivores (Table 1) (28). In a recent study from our laboratory, the mean Omega-3 Index was 3.7% in 167 individuals who had been vegans for an average of 12 y (29). A larger series including omnivores, vegetarians, and vegans was studied by Rosell et al (30). Plasma proportions (percentage of total fatty acids) of EPA and DHA were reduced in a stepwise manner by eating pattern, but ALA proportions did not change (Figure 1).

EFFECTS OF n–3 FATTY ACIDS ON THE OMEGA-3 INDEX IN VEGETARIANS

Although few studies have directly tested the hypothesis, vegetarians and vegans appear to respond to supplemental EPA and DHA as do omnivores. A relatively low dose of DHA (200 mg/d from algal oil) for 3 mo increased plasma phospholipid DHA content by ~30% (Figure 2) (27). In a study focusing on RBC membranes, Geppert et al (31) tested the effects on the Omega-3 Index from 8 wk of treatment with an algal oil providing 800 mg DHA/d in 52 vegans (compared with 51 vegans who received placebo). The index increased from 4.8% to 8.4% in the DHA group (P < 0.001; no change with placebo). RBC EPA content increased from 0.41% to 0.48% [reflecting minor retroconversion of DHA to EPA (32)] and DHA content increased from 4.4% to 7.9%. By comparison, Milte et al (33) supplemented healthy omnivores with 1 g of DHA/d from tuna oil, and after 8 wk RBC DHA content had increased from 4% to 6.5%. Thus, RBC DHA content in the vegetarians in the Geppert et al study responded at least as well if not better to an increased DHA intake than did omnivores in Milte et al’s study.

VEGETARIAN SOURCES OF n–3 FATTY ACIDS

If increases in the Omega-3 Index in a vegetarian diet did in fact afford additional health benefits, then how might this be accomplished without eating fish or fish oils? The most obvious approach would be to consume more ALA (and less linoleic acid) (34). It is the amount of ALA that is consumed, not the ratio of ALA to linoleic acid, that determines the amount of EPA that is produced (35). Even though EPA concentrations can be somewhat increased by this approach, DHA concentrations can not. A recent study by Dewell et al (36) in omnivores illustrates this point (Figure 3). They compared the effects of placebo with low- and high-dose ALA (2.2 and 6.6 g/d, respectively) and low- and high-dose fish oil (EPA: 0.7 and 2.1 g/d, respectively) over 8 wk in 100 subjects with metabolic syndrome. On a per-gram ALA (or EPA) basis, RBC EPA increased by ~12% with ALA and by ~174% with preformed EPA. Neither of the ALA doses increased RBC DHA. In fact, the higher dose of ALA nonsignificantly lowered RBC DHA (from 4.1% to 3.6%). The net effect on the Omega-3 Index was null for both ALA doses.

A novel way to improve blood n–3 content is to consume plant-based n–3 fatty acids that are more readily converted into the longer-chain metabolites. One such product is a genetically engineered variety of soybean oil containing the n–3 fatty acid stearidonic acid (SDA, 18:4n–3). SDA is the first product in the pathway from ALA to EPA and is synthesized by the rate-limiting enzyme in the pathway, δ6 desaturase. Intake of SDA-enriched soybean oil (Soyomega; Monsanto Company) has been shown to significantly increase concentrations of EPA (but not DHA) in blood and tissues in humans (37). Products such as this could, in theory, provide unlimited amounts of n–3 fatty acids in the human diet (36); and, much like the fortification of salt with

<table>
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<th>Fatty acid</th>
<th>Linoleic</th>
<th>AA</th>
<th>EPA</th>
<th>DHA</th>
<th>Omega-3 Index ²</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of total fatty acids</td>
<td>% of total fatty acids</td>
<td></td>
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<td></td>
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<tr>
<td>Omnivores</td>
<td>9.8</td>
<td>13.8</td>
<td>0.55</td>
<td>3.90</td>
<td>4.45</td>
</tr>
<tr>
<td>Vegans</td>
<td>11.6*</td>
<td>14.2</td>
<td>0.22*</td>
<td>2.04*</td>
<td>2.26*</td>
</tr>
</tbody>
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1 Data are from reference 28. *P < 0.001. AA, arachidonic acid; RBC, red blood cell.
2 RBC EPA+DHA as a percentage of total RBC fatty acids.
iodine reduced the incidence of goiter, adding effective n–3 fatty acid precursors to commonly consumed foods could remediate the chronically low n–3 fatty acid concentrations that are so common in Western cultures. At present (October 2013), Monsanto has entered into a partnership with DSM Nutritional Products to market the product. Furthermore, efforts are underway to expand land plant bioengineering so as to produce not SDA but EPA and DHA (39).

There are certain strains of microalgae that naturally produce EPA and DHA (40). The oils harvested from these single-celled organisms are used to fortify infant formulas with DHA (to achieve amounts similar to those in human breast milk). Dietary supplements containing these “marine” n–3 fatty acids are now available to consumers and can provide vegetarians with pre-formed EPA and DHA (Life’sDHA; DSM Nutritional Products). A bioengineered oleaginous yeast (Yarrowia lipolytica) produces an oil rich in EPA (41) and was, for a time, available as a supplement (New Harvest; DuPont); it is now, however, discontinued and unavailable. Although still in its infancy, the industrial production of EPA and DHA from nonfish sources will someday provide vegetarians and omnivores alike with a virtually infinite supply of these important nutrients.

CONCLUSIONS

Vegetarian and vegan dietary patterns are associated with reduced risk of cardiovascular disease, and at present, we have few data to confirm that this risk may be reduced even more by the provision of marine n–3 fatty acids. This would be an important question for future researchers to examine. Achieving a cardioprotective Omega-3 Index (ie, >8% of RBC fatty acids as EPA+DHA) is challenging for individuals who will not eat oily fish, the primary dietary source of these fatty acids. Some non-animal sources of n–3 fatty acids are appearing in the marketplace, but they are expensive (~10 times the cost of equivalent fish oils) and not widely available. Increasing demand for such products will undoubtedly increase supply and reduce costs as more individuals begin to appreciate the health benefits of both n–3 fatty acids and a vegetarian diet.

REFERENCES


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