Arachidonic acid concentrations in patients with Crohn disease

Dear Sir:

We read with interest the work by Jeppesen et al (1) examining the fatty acid content of plasma phospholipids in patients with malabsorption and patients receiving home parenteral nutrition (HPN). In that article, patients with fat malabsorption were subgrouped according to the severity of malabsorption (fat malabsorption ≤50% and fat malabsorption >50%), whereas patients receiving HPN were grouped according to whether they received parenteral lipid. The control subjects were healthy volunteers. Most of the patients in the non-HPN groups (17 of 20) had Crohn disease and 11 of 20 patients in the HPN groups had Crohn disease.

We would like to draw attention to the significant differences, not discussed in the text, in percentage plasma phospholipid arachidonic acid (AA; 20:4n–6) among the groups. AA, along with eicosapentaenoic acid (20:5n–3), serves as an eicosanoid precursor; its deficiency is responsible for many of the clinical consequences of essential fatty acid deficiency. Non-HPN patients without major fat malabsorption and HPN patients receiving lipid had strikingly higher AA concentrations than did control subjects (7.8%, 10.4%, and 11.7%, respectively; both P < 0.05). Patients with short-gut syndrome and severe malabsorption and HPN patients not receiving lipid had values similar to those of control subjects (8.1% and 8.3%, respectively), presumably reflecting relative dietary deficiency of the essential fatty acid precursor, linoleic acid. Generally, AA concentrations are tightly controlled and stable across a wide range of linoleic acid intakes above a maintenance intake. AA concentrations are reduced only in a limited number of conditions, including classic essential fatty acid deficiency, prematurity or end-stage liver disease (in which hepatic enzyme immaturity or pathologic damage, respectively, prevents elongation and desaturation to AA), and increased dietary intake of eicosapentaenoic acid, which inhibits formation of AA from precursors and competes with AA for tissue incorporation (2). Elevated AA relative to linoleic acid is rarely found to be related to diet because AA, which can enter phospholipids directly (3), is usually such a small dietary component.

We wonder whether this elevation in AA might represent a proinflammatory state and question whether provision of lipid to HPN patients as a means of normalizing linoleic acid concentrations might exacerbate the inflammation underlying Crohn disease. It would be interesting to consider patients with Crohn disease stratified for extent of malabsorption separately from other patients with fat malabsorption; such stratification has never been performed stringently. The presence of a relative increase in the ratio of AA to linoleic acid in the intestinal mucosa of patients with Crohn disease has been documented and the etiologic importance of this finding in the development of local inflammation considered (4). Thus, this parallel finding of Jeppesen et al is a potentially important observation. If it can be confirmed that patients with Crohn disease who are not deficient in essential fatty acids (either because of only mild-to-moderate malabsorption or because of parenteral fat therapy) have an overabundance of plasma phospholipid AA, we must consider the possibility that abnormal fatty acid regulation might play an important role in the pathology of Crohn disease. This hypothesis is strengthened by the finding that fish oil, possibly by inhibiting AA formation and altering eicosanoid production, can maintain clinical remission in patients with Crohn disease (5).

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REFERENCES

Reply to KC McCowen, PR Ling, and BR Bistrian

Dear Sir:

We wish to thank McCowen et al for their interest in our article and for addressing an intriguing hypothesis. We agree that it would be interesting to attempt to consider patients with Crohn disease, stratified for extent of malabsorption, separately from other patients with fat malabsorption in terms of the concentra-
tion of the eicosanoid precursors arachidonic and eicosapentaenoic acids. However, the small number of patients investigated in this study would not allow such a stratification.

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Whole grains and coronary heart disease

Dear Sir:

The report in the September issue by Liu et al (1) concerning the Nurses’ Health Study concluded that the strong inverse association between whole-grain intake and coronary heart disease was to a large degree not explained by the constituents of whole grains thought to be protective. The accompanying editorial (2) essentially concluded the same.

One constituent and confounder not considered in this study, nor in most studies regarding coronary heart disease and homocysteine’s potentially detrimental role therein, is betaine (trimethylglycine). Betaine, although once considered a vitamin-like component (3), is also endogenously synthesized from choline. It is found in whole grains and represents >0.5% of wheat bran and wheat germ but only 0.06% (and often <0.02%) of white wheat flour. Choline, the endogenous betaine precursor, represents =0.2%, 0.3%, and 0.08% of wheat bran, wheat germ, and white flour, respectively (3).

Betaine is the only non-vitamin-dependent homocysteine-lowering agent that methylates homocysteine to form methionine through a pathway that appears to be unhindered by any known genetic enzyme dysfunctions. Betaine is also considered a lipotrope, being related to lecithin and choline, and was used as such—in combination with B vitamins and liver extract—in promising clinical coronary heart disease research done by Lester M Morrison in the 1950s (4, 5).

The almost general omission in research of betaine as a cardioprotective variable or as a confounder during the past 40 y or so is largely due to the absence of food tables that include betaine. In addition to whole grains, betaine is found in liver, eggs, and seafood. It is also found in plants such as beets and spinach, in which its role appears to be to increase resistance to drought and saline growing conditions.

The development of food tables that include betaine and its endogenous precursor choline is urgently needed to enable these confounders to be included in cardiovascular research and to close the gap of unrecognized confounders (1).

Eddie Vos

REFERENCE

Reply to E Vos

Dear Sir:

We appreciate Vos’ comments on our article and completely agree that the development of a database for betaine—and for choline—is a high priority. Other constituents of whole grains, such as magnesium, may also be important for maintaining cardiovascular health (1) and warrant further careful examination. Additionally, focusing on individual components of whole grains may not be adequate to elucidate their role in disease prevention; we also need to consider interactions among these components as well as the physical properties of and the nature of the starches in these foods (2).

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REFERENCES
Erratum


Footnote 3 to Table 1 is incorrect. The footnote should read as follows: Cumulative olive oil consumption index calculated on the basis of adherence to Greek Orthodox Lent (see Methods).

Erratum


Although the amino acids are correct, the nucleotide sequence shown in Table 4 for exon 4 is incorrect. The correct nucleotide sequence is shown below. Additionally, the mutation of exon 4 is located at amino acid position 75, and not 74 as described in the article. Note that the correct sequence of exon 4 was submitted to the EMBL database (accession number AF025335).

<table>
<thead>
<tr>
<th>Exon 3, nucleotides</th>
<th>Exon 4, nucleotides</th>
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<tbody>
<tr>
<td>1278–1286</td>
<td>1545–1553</td>
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</tbody>
</table>

Control subject

Nucleotide sequence

AAC AAC GTC

Amino acid

Ile

GTG GGC ACC

Gly

Sibling A

Nucleotide sequence

AAC AAC GTC

Amino acid

Asn

GTG GAC ACC

Asp

Sibling B

Nucleotide sequence

AAC AAC GTC

Amino acid

Asn

GTG GAC ACC

Asp

Mother

Nucleotide sequence

AAC AAC GTC

Amino acid

Asn

GTG GGC ACC

Gly

1 Shown is the T-to-A substitution at nucleotide 1282 in exon 3 for the siblings and the mother and the G-to-A substitution at nucleotide 1549 in exon 4 for the siblings only. The nucleotide numbering is according to reference 3.

2 Amino acid position 41.

3 Amino acid position 75.
Erratum


The second full sentence on page 302S should read: “Fifty-one percent of the women in the alcohol group consumed alcohol during the 2-wk period before delivery, drinking a 2-d average of 42.88 mL/d (range: 4.14-81.62 mL/d) for an average of 2 drinking days (range: 1-4 d; data not shown) within that 2-wk period.” The following entries in Table 1 for the alcohol group were incorrect: for alcohol consumed in the periconceptional period, the mean value should be 56.19, not 56.9; for alcohol consumed during pregnancy, the value in parentheses should be 12.42, not 7.2; and for the total amount of alcohol consumed during pregnancy, the value in parentheses should be 2658.61, not 2568.61.