**Long-chain polyunsaturated fatty acids and diabetes mellitus**

Dear Sir:

The recent report in the Journal by Salmerón et al (1) suggests that replacing 2% of energy from *trans* fatty acids isoenergetically with polyunsaturated fatty acids (PUFAs) would lead to a 40% lower risk of type 2 diabetes. These authors also suggested that intakes of total fat and monounsaturated fatty acids are not associated with the risk of type 2 diabetes, but that intake of *trans* fatty acids is positively associated with the risk in women. This work is supported by evidence indicating that increased intakes of long-chain PUFAs (LCPUFAs) reduce insulin resistance and, thus, decrease the risk of type 2 diabetes. Ginsberg et al (2) showed that the number of insulin receptors decreases when Ehrlich cells, which show all the binding characteristics of mammalian insulin receptor, were enriched in monounsaturated fatty acids and increases when enriched in PUFAs. In male Wistar rats, fish oil intake not only results in a significant decrease in plasma total and LDL cholesterol but also in normoglycemia, dose-dependent hypoinsulinemia, a dose-dependent increase in glucose utilization and clearance in vivo, and an increase in insulin sensitivity (3). Breast-fed infants have a significantly higher percentage of docosahexaenoic acid (DHA) and LCPUFAs in muscle phospholipids and lower plasma glucose concentrations than do formula-fed infants (4). Children who have either never or not recently been breast-fed show a significantly inverse correlation between fasting plasma glucose and the percentage of both DHA and total LCPUFAs (4). Thus, higher LCPUFA concentrations in the skeletal muscle membrane are associated with lower fasting plasma glucose concentrations. These results are interesting because it is known that low concentrations of DHA and other LCPUFAs in skeletal muscle membrane phospholipids are associated with insulin resistance and obesity in adults. Furthermore, a high-fat, low-carbohydrate intake was shown to reduce the ability of insulin to inhibit endogenous glucose production (5), whereas substitution of dietary saturated for monounsaturated fat was shown to impair insulin sensitivity in healthy men and women (6). On the other hand, insulin sensitivity was shown to be correlated positively with the percentages of arachidonic acid (AA), the total percentage of 20–22-carbon PUFAs, and the ratio of the percentage of AA to the percentage of dihomo-γ-linolenic acid in the muscle phospholipid fraction (7). This suggests that the fatty acid composition of muscles and dietary fatty acids modulate the action of insulin. There is also evidence to suggest that LCPUFAs play a role in type 1 diabetes.

We observed that prior treatment of Wistar rats with oils rich in eicosapentaenoic acid (EPA), DHA, AA, and γ-linolenic acid (GLA) prevents the development of alloxan-induced diabetes mellitus (8). Additionally, prior oral administration of 99–99.9% pure GLA, AA, EPA, and DHA completely prevents the occurrence of alloxan-induced diabetes mellitus in experimental animals (9). These findings suggest that LCPUFAs protect β cells from the cytotoxic actions of alloxan. In vitro studies showed that alloxan-induced apoptosis of β cells can be prevented by GLA, AA, EPA, and DHA (9). Earlier studies with LCPUFAs concentrated on the effects of these fatty acids to prevent or arrest the complications of diabetes mellitus. Conversely, we showed that LCPUFAs actually protect β cells from the cytotoxic effects of alloxan. This finding, coupled with the observation that cod liver oil (a rich source of EPA and DHA) consumed during pregnancy is associated with a reduced risk of type 1 diabetes in the offspring, indicates that LCPUFAs protect against type 1 diabetes (10). Tumor necrosis factor α (TNF-α) plays a significant role in insulin resistance and is involved in pancreatic β cell damage; therefore, TNF-α participates in the pathogenesis of both type 1 and type 2 diabetes (reviewed in 8, 9, 11). LCPUFAs inhibit the production of TNF-α both in vitro and in vivo (reviewed in 11), which may explain the beneficial effect of LCPUFAs in both type 1 and type 2 diabetes. The results of Salmerón et al (1) lend further support for the role of LCPUFAs in the pathogenesis of diabetes. In view of these findings, it would be prudent to study whether supplementation with LCPUFAs can protect high-risk individuals from diabetes.

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Comments on the new dietary reference intake for vitamin E

Dear Sir:

I am writing in response to the editorial by Traber (1) and the article by Horwitt (2). I agree with Horwitt that the “50% increase in the recommended dietary allowances for vitamin E is not supported by any new data.”

Traber states that the new dietary reference intake is based on the in vitro erythrocyte hemolysis test because this test was used in Horwitt’s Elgin Project studies. The peroxide hemolysis test entails a highly variable procedure, which Horwitt (3) clearly emphasized. He stated, “the concentration of the hydrogen peroxide, the rate at which it is added to the erythrocyte suspension, the temperature, and the elapsed time of incubation all can have large effects on the hemolysis obtained.” He also pointed out that “one can easily choose conditions at which all normal blood would hemolyze or, conversely, where no deficient blood would hemolyze.”

Other investigators have also reported the many variables that can affect the hemolysis test (4). Horwitt (3) further stated that “this choice [0.5 mg/100 ml] is fortuitous since one does not obtain signs of a more rapid erythrocyte turnover in subjects that have as much as 0.5 mg/100 ml of tocopherol in their blood.”

Traber justifies the elimination of γ-tocopherol in the assessment of dietary vitamin E because there is no known transport protein for this vitamer. Because γ-tocopherol has been shown to have biological activity in all species tested (5), it seems inconceivable that humans should not benefit from this form of vitamin E. Healthy human blood contains significant concentrations of γ-tocopherol, even without (presumably) a specific transport protein. In summary, the establishment of a dietary reference intake for vitamin E on the basis of “the best data currently available,” as Traber states, should not discount the best data of the past.

John G Bieri

Reply to JG Bieri

Dear Sir:

This comment is in response to the letter from Bieri, a well-recognized leader in the vitamin E field and a member of the committee that set the 1989 recommended dietary allowances (RDAs; 1). The new dietary reference intakes (DRIs) take into account not only deficiency symptoms but also the amounts of vitamins and minerals that provide an optimum benefit across the life span. The “health benefit of vitamin E for humans” is the basis for the 2000 DRI for vitamin E (2). The in vitro peroxide-dependent erythrocyte hemolysis test was chosen as a marker of vitamin E status because vitamin E–deficient children with neurologic abnormalities were shown to have erythrocytes that are sensitive to peroxide-induced hemolysis in vitro and a faster in vivo erythrocyte turnover (3). All of these responses, including the neurologic abnormalities, were reversed or ameliorated by supplements containing α-tocopherol (2). The erythrocyte hemolysis test was also used in the studies carried out by Horwitt et al (4) to evaluate vitamin E status in humans who had consumed vitamin E–deficient diets for >5 y and were then given vitamin E supplements containing either RRR- or all-rac-α-tocopherol. These data were used to set both the 1968 RDA (30 IU vitamin E) and the 2000 DRI (15 mg 2R-α-tocopherol, or 22 IU RRR-α-tocopherol, or 33 IU all-rac-α-tocopherol). The 2000 DRI takes into account that all-rac-α-tocopherol has one-half, not two-thirds, the activity of RRR-α-tocopherol.

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Admittedly, the erythrocyte hemolysis test is flawed in that it is critically dependent on assay conditions. However, the 1989 RDA for vitamin E was based on the observation that humans do not readily show symptoms of vitamin E deficiency; therefore, the usual amount of dietary vitamin E must be adequate. Currently, this level of evidence is insufficient to set an RDA; dietary intakes could be used to set an AI (average intake).

γ-Tocopherol was included in the forms of vitamin E that met the 1989 RDA because of its abundance in the American diet. The justification for its biological activity is that high amounts fed to vitamin E–deficient pregnant rats prevent fetal resorption (5). Unfortunately, these tests were carried out >20 y ago, when the methods used to detect contaminating α-tocopherol were not as sensitive as today’s techniques. Therefore, the extent to which α-tocopherol contaminated the γ-tocopherol used in the diets is unknown. This is especially important in light of the discovery that the α-tocopherol transfer protein (α-TTP) is critically important in the rodent uterus during pregnancy (6). Hepatic α-TTP maintains plasma α-tocopherol by facilitating its export from the liver to the periphery via the plasma lipoproteins; α-TTP binds α-tocopherol but has little affinity for γ-tocopherol (7). Humans with a defect in the α-TTP gene become deficient in vitamin E (8), as do α-TTP knockout mice (6, 9). Importantly, administration of α-tocopherol reverses human vitamin E deficiency symptoms, proving that humans require α-tocopherol.

Most of the postulated health benefits of γ-tocopherol are based on in vitro studies testing whether γ-tocopherol nitration might protect against peroxynitrite injury. Ohrvall et al (10), however, reported that circulating γ-tocopherol but not α-tocopherol concentrations were low in patients with coronary heart disease (CHD), suggesting that γ-tocopherol might be protective. Lemcke-Norojarvi et al (11) showed in Swedish women that changing the usual Swedish diet (low in γ-tocopherol) to one containing corn oil (high in γ-tocopherol) raised γ-tocopherol by 64% but had no effect on serum α-tocopherol. Furthermore, Ohrvall et al (12) showed in a double-blind crossover trial that a diet containing unsaturated fat (rapeseed oil) increased circulating α-tocopherol by 7% and γ-tocopherol by 23%, whereas a diet containing saturated fat decreased α-tocopherol by 5% and γ-tocopherol by 37%. Taken together, these data suggest that if patients with CHD switch to an unsaturated oil, such as corn oil, circulating γ-tocopherol will increase but α-tocopherol will be unchanged. Perhaps, more importantly, the change from saturated to unsaturated fat will lower serum cholesterol and thereby CHD risk. Thus, serum γ-tocopherol may be a marker of a vegetable oil–containing diet that is lower in saturated fat and higher in unsaturated fat. These dietary changes lead to lower circulating cholesterol that will lower CHD risk. Thus, γ-tocopherol itself does not necessarily decrease CHD risk. With respect to the 2000 DRI, γ-tocopherol may have health benefits, but as of yet, these have not been shown in humans; therefore, only α-tocopherol meets the human vitamin E requirement.

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