equivalency defined by the WHO/FAO in 1967 (6) (in which 1 IU = 0.3 μg retinol or 0.6 μg β-carotene) addresses only bioconversion (the observation that it would take ≈2 μg β-carotene to form 1 μg of retinol within a human cell) (2). Thus, we agree with Drake et al that the IU by itself does not address factors such as the extent of absorption before bioconversion of carotenoids from differing plant sources, cooking processes, levels of nutritional status, or the presence of factors that enhance absorption (eg, lipids). However, the matter of bioavailability was included indirectly when recommended intakes were set in the United States on the basis of the assumption that half of the dietary vitamin A would come from animal sources and half from less bioavailable plant sources (7).

In the most recent review of vitamin A reference values from the Food and Nutrition Board (FNB) (4) as part of establishing dietary reference intakes (DRIs) for Canada and the United States, bioavailability factors were updated as RAEs. Whereas the current USDA database still includes entries for vitamin A in IU because IU is the unit used in nutrition labeling, the SR also includes vitamin A content for each food item in RAE and gives values in μg for retinol, β-carotene, α-carotene, and β-cryptoxanthin. These are the values that should be used for nutrition studies.

Today in the United States, we are faced with nutrition labeling regarding vitamin A that is essentially frozen in time via regulation by the FDA: the DV for vitamin A is 5000 IU. This value was the adult RDA (7) when voluntary nutrient labeling was initiated in 1973, and it became the US RDA. In 1993, with the implementation of mandatory nutrition labeling, the FDA opted to continue the use of the US RDA values for DVs. Because the USDA nutrient database is expected to support all federal programs, the FDA has relied on the inclusion of IU values in the database for foods for use by food manufacturers who must label their food products in IUs. In the documentation for the database (1) (available at http://www.nal.usda.gov/fnic/foodcomp/search), the IU equivalency is discussed; the documentation indicates that the IU equivalency is provided for nutrition labeling and includes a discussion of the RAE and the change from earlier values in RE.

It is unfortunate that the DV on the Nutrition and Dietary Supplement Facts Panels is still based on the 1968 RDA of 5000 IU, but the USDA cannot change the definition of the IU to directly take into account bioavailability, as Drake et al urge be done. The IU is defined by the WHO/FAO, not the USDA. Drake et al propose that it is scientifically appropriate to use the RAE equivalency to convert food values that are given in IUs to reduced-value IUs based on Table 4-3 in the DRI report (4). However, the FNB did not redefine the IU. Instead, it established REs and then RAEs. The purpose of the footnote on Table 4–3 is to allow conversion from IUs to RAEs.

The good news in moving toward elimination of the IU is that the US Department of Agriculture has just published in the Federal Register a long-awaited notice requesting comments on updating the DV (8). The questions focus on how best to update the DVs with the DRIs or other standards, and they specifically ask whether IUs should be continued (not only for vitamin A, but for vitamin E as well). Thus, this is the right time for scientists and clinicians alike to bring up these issues of confusion and dated science by responding to the FDA’s request for comments, which we strongly urge Drake et al and others with concerns about nutrition labeling to do.

None of the authors had a personal or financial conflict of interest.

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REFERENCES

Homocysteine, vitamins, and vascular disease prevention: more negative results

Dear Sir:

With much interest we read the article by McCully (1), which implies a potential role of homocysteine reduction in the primary prevention of cardiovascular disease (CVD). Although the author did note the negative results of the homocysteine reduction clinical trials, he further raised doubts about their conclusion because of the lack of statistical power, the length of the trials required, and the fortification of the North American food supply with folic acid. We believe that the evidence supporting any benefit of homocysteine reduction, whether in primary or secondary CVD prevention, is getting weaker and weaker.

In addition to the negative results of the 3 major studies mentioned in McCully’s article (VISP, NORVIT, and HOPE2), negative results from the HOST trial have also been published (2). The HOST trial (2)
was designed to assess the effects of a reduction in homocysteine concentrations on mortality and vascular outcomes in 2056 patients with renal disease. Participants with advanced chronic kidney disease (estimated creatinine clearance of 30 mL/min, or 0.50 mL/s) or end-stage renal disease and with homocysteine concentrations of ≥15 μmol/L, were randomly assigned to receive 40 mg folic acid, 2 mg cyanocobalamin (vitamin B-12), and 100 mg vitamin pyridoxine hydrochloride (vitamin B-6) daily or a placebo. Despite a 26% reduction in homocysteine concentrations (achieved with a dose of folic acid substantially in excess of that required to achieve a maximal reduction in homocysteine), the HOST study reported no significant reduction in the primary endpoint of all-cause mortality and no significant reductions in any of the secondary outcomes, which included myocardial infarction, stroke, and amputations. Considering the high baseline homocysteine concentration of participants in the HOST study, the argument that the negative results in the published clinical trials were due to the already lower serum homocysteine concentrations in the general population, because of fortification of the North American food supply with folic acid, is invalid.

More negative results have been also published from a recent meta-analysis of randomized controlled trials, which included 165 relevant reports and 12 randomized controlled trials that compared folic acid supplementation with either placebo or usual care for a minimum duration of 6 mo and with clinical cardiovascular disease events reported as the endpoint. In this meta-analysis, the relative risk (RR) of coronary heart disease (CHD) was 1.04 (95% CI: 0.92, 1.17) and of stroke was 0.86 (95% CI: 0.71, 1.04) (3). When these results were updated with the results of the HOST trial, the overall inverse-variance weighted odds ratio per each 3-μmol/L reduction in homocysteine concentration, for a mean duration of treatment of 3.1 y, was 1.00 (95% CI: 0.92, 1.09) for CHD events (n = 12 trials) and 0.88 (95% CI: 0.78, 1.00) for stroke (n = 9 trials) (4). Given the large sample size of the abovementioned meta-analysis, the issue of low power should be irrelevant. It is worth mentioning that, although the HOPE-2 study did report a significant reduction in stroke, as mentioned in McCully’s article, this was a secondary outcome.

All of these negative results make doubtful the evidence in support of a possible reduction in CVD risk through a reduction in homocysteine concentrations. The argument that a reduction in homocysteine concentrations via vitamin B supplementation is helpful in the primary prevention of CVD needs to be revised. It is well known that a reduction in established CVD risk factors, such as hypercholesterolemia, smoking, obesity, hypertension, and diabetes, results in a more significant reduction in CVD as a secondary prevention approach than as a primary prevention approach. Why then should we expect the opposite from homocysteine if it is really a causal risk factor for CVD and not just a disease marker?!

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REFERENCES

Reply to EZ Soliman and OA Shalash
Dear Sir:

In their letter concerning the negative results of the HOST trial of homocysteine reduction by high-dose B vitamins in renal failure patients (1) and the recent meta-analysis by Bazzano et al (2), Shalash and Soliman comment that “all of these negative results are making the evidence for a possible benefit of reducing CVD through reducing homocystein doubtful.” They further suggest that possible primary prevention by this approach “needs revision” because blood homocysteine may be a marker of disease rather than a causal risk factor.

In their recent meta-analysis of 8 intervention trials with supplemental folic acid, which involved a total of almost 17 000 subjects, Wang et al (3) concluded that this approach “significantly reduced the risk of stroke by 18%.” They further found that a greater beneficial effect was seen in those trials with a treatment duration of >36 mo (29% reduction), a decrease in the concentration of homocysteine of >20% (23% reduction), no fortification or partly fortified grain (24% reduction), and no history of stroke (25% reduction). They also commented that the meta-analysis by Bazzano et al (2) showed a significant reduction in stroke after removal of the VISP trial from the analysis, because the VISP trial was conducted in individuals with a history of stroke. In the VISP trial, exclusion of subjects with renal failure, subjects with malabsorption of vitamin B-12, and subjects with high levels of vitamin B-12 from non-study supplementation yielded significant reductions in stroke, coronary disease, and mortality from B vitamin intervention in 2155 subjects over a 2-y period (4).

In their commentary on “judging causality in the face of inconclusive trial evidence,” Wald et al (5) examined evidence from the meta-analysis of cohort studies, the genetic polymorphism studies, and the randomized intervention trials. They concluded that “the summary estimate from the trials is consistent with a short term protective effect [of homocysteine lowering] of 12% on ischemic heart disease events and 22% on stroke, or a larger long term effect.”