

The bioavailability bugaboo^{1,2}

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It is no longer sufficient for nutritionists to prevent deficiency symptoms; they are now charged with defining nutrient intakes for optimal health (1). In this context, the term “chronic disease” is invoked frequently and epidemiologic data are touted to show that diets high in fruit and vegetables are beneficial for reducing the risk of heart disease and cancer. But when single dietary components are tested in intervention trials, the results are sometimes extraordinarily promising, eg, the 77% decrease in second heart attacks in patients with coronary disease given vitamin E (2); sometimes extraordinarily disastrous, eg, the 18% increase in lung cancer in smokers given β -carotene supplements (3); or simply equivocal (4). As Block (5) pointed out, clinical trials are designed to test drug efficacy, not long-term nutrient intakes. If so, what is the appropriate method for the nutritionist?

Traditionally, the reversal of deficiency symptoms was used to assess nutrient requirements. As we became more skilled in biochemistry and molecular biology, the precise physiologic roles of nutrients became the standard for setting requirements—quantities that optimize specific physiologic functions. This approach is most likely to be successful for answering the question, How much of a nutrient is needed for optimal health? Here enters the major problem of, What is the bioavailability of a nutrient?

Bioavailability is defined as the plasma concentration of a water-soluble drug given orally compared with the concentration when the drug is given intravenously. The transfer of this concept from pharmacology to nutrition has been successful, at least in the case of vitamin C, a water-soluble nutrient (6). But, for fat-soluble nutrients, bioavailability is difficult to assess because the nutrient cannot be given intravenously, so relative bioavailability (the change in plasma concentration in response to a test meal) is often measured.

Part of the difficulty of assessing the bioavailability of fat-soluble nutrients is the complexity of the absorption process. Fat-soluble nutrients must be solubilized in micelles, a process that depends on adequate bile and pancreatic secretions. Subsequently, the micelles transfer their contents to the intestinal cells, where these nutrients are packaged in chylomicrons, secreted into the lymph, and transported to the liver. Once the chylomicron remnant arrives at the liver, most fat-soluble nutrients then depend on liver mechanisms for disposition. Vitamins A and E provide contrasting examples of nutrients with protein-mediated fates. The retinol binding protein binds retinol, is secreted into the plasma, and acts as a plasma carrier protein. In contrast, the α -tocopherol transfer protein (α -TTP) binds and transfers α -tocopherol within the hepatocyte, but facilitates α -tocopherol secretion only from the liver for transport in plasma lipoproteins;

α -TTP itself is not found in plasma. This makes estimation of the relative bioavailability of α -tocopherol more difficult because plasma α -tocopherol concentrations depend on plasma lipid concentrations.

But what about those fat-soluble nutrients that do not have transfer proteins? How are “beneficial” plasma concentrations achieved? Again, vitamin E provides an interesting example. Humans with a genetic defect in α -TTP have severe vitamin E deficiency—extremely low plasma and tissue vitamin E concentrations and progressive peripheral neuropathy (7, 8). When given supplements containing α -tocopherol in amounts 100 times the recommended dietary allowance of vitamin E, these people can maintain normal plasma and tissue α -tocopherol concentrations and the neurologic symptoms are reversed or halted. If supplementation is discontinued, the plasma concentrations of these individuals decrease within days to deficient levels—a phenomenon never seen in healthy subjects. These findings imply that, in the absence of α -TTP, the vitamin E “default pathway,” and perhaps that of other fat-soluble nutrients, is rapid plasma removal and biliary excretion. These data also suggest that continued intake of large amounts of other fat-soluble nutrients will allow plasma concentrations to remain elevated.

It is obvious that fat-soluble nutrients require some fat for absorption and that nature does not incorporate fat-soluble nutrients into foods without fat. However, that does not limit food manufacturers (eg, manufacturers of vitamin E-enriched fat-free mayonnaise or vitamin D-enriched fat-free milk) or plant geneticists [eg, those working with β -carotene-enriched rice (9)] from increasing the food contents of fat-soluble nutrients without adding fat. Roodenburg et al (10) attempted to study the question of how much fat is necessary. They studied the relative bioavailability of some carotenoids and vitamin E in humans and reported that lutein esters, but not other fat-soluble nutrients, are dependent on a higher fat content (36 g compared with 3 g) of a hot meal for increased relative bioavailability. Subjects consumed low-fat breakfasts and lunches and high- or low-fat dinners that were varied by changing the fat contents of experimental spreads. In this split-plot design, 1 group received a

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placebo-containing spread during the two 7-d experimental periods of high or low fat consumption, whereas the other 3 groups received spreads supplemented with α -tocopherol, α - and β -carotenes, or lutein esters. When these fat-soluble nutrients were dissolved in fat and consumed as part of a hot meal, the effect of 3 g fat was equal to that of 36 g on plasma concentrations of α -tocopherol and α - or β -carotenes. Lutein bioavailability, however, was improved with high fat intakes. Lutein was provided as lutein esters, which likely required hydrolysis mediated by lipases (11). Perhaps the additional fat intake stimulated pancreatic lipase secretion and improved hydrolysis of the lutein esters. An interesting addition to the study would have been to include α -tocopheryl acetate, a form commonly used in vitamin E supplements or as a food fortificant, because it too must be hydrolyzed before absorption.

We are still left with the question of how much fat is necessary for absorption of fat-soluble nutrients not dissolved in 3 g fat eaten as a spread, but naturally present as a component of food or added during its manufacture, perhaps without fat. We also face the quandary of fat-soluble nutrient interactions. Roodenburg et al (10) administered the fat-soluble nutrients individually, yet these nutrients are usually found in combination. Worse yet, lutein and carotenes appear to adversely affect each other's absorbability (12). Diet composition is also a factor. The nutrient intake of one fat-soluble nutrient does not dictate the intakes of the others—a low-fat diet, high in fruit and vegetables, increases carotenoid intakes but decreases α -tocopherol intakes (13, 14). Study of bioavailability and nutrient interactions also needs to be extended to include flavonoids and other phytochemicals because concentrations necessary to produce favorable effects of these nutrients in tissue culture may not be achievable *in vivo*.

Thus far we have considered variables in foods, but variability in the individual consuming the foods adds to the bioavailability problem. Plasma concentrations of fat-soluble nutrients carried in lipoproteins also depend on plasma lipoprotein concentrations. Thus, a subject with a high plasma lipid concentration has the ability to transport more of the fat-soluble nutrient and as a result will have a higher plasma concentration, but is that nutrient available to tissues? And what about the subjects' routine food choices? Does a person who usually consumes several servings of fruit and vegetables respond to a test meal differently from one who avoids these foods?

Does the size of a nutrient dose matter? Does diet composition or meal frequency matter? Does the food matrix in which the nutrient is bound materially affect the nutrient's bioavailability? And if so, as seems likely, what happens if the food is puréed, juiced, cooked, or both cooked and mashed? This bioavailability problem seems to leave us with endless unanswered questions

and a tremendous amount of work to do. However, bioavailability of specific nutrients is a cornerstone to determining the amount of any given nutrient for optimal health. 

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