Bioavailability of Nutrients and Other Bioactive Components from Dietary Supplements

Factors in Aging that Effect the Bioavailability of Nutrients

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ABSTRACT Until a few years ago, little was known about bioavailability of micronutrients in elderly humans. It was assumed by many basic investigators and geriatricians that malabsorption of both macronutrients and micronutrients was a common problem among elderly persons. We now know that this is not the case; elderly persons who malabsorb macronutrients do so because of disease, not because of age. This report will be divided into three sections. The first section focuses on the general principles of absorptive processes in elderly persons. The second section focuses on the bioavailability of specific micronutrients in elderly persons, with specific examples of “problem” nutrients. The third section lays out a proposed research agenda for studying the bioavailability of nutrients and other active components of dietary supplements in elderly persons. J. Nutr. 131: 1359S–1361S, 2001.

Because of a large reserve capacity of both the pancreas and small intestine, elderly persons do not maldigest or malabsorb macronutrients. It has been shown that slight declines in both pancreatic secretion and small intestine absorptive capacity occur after repeated stimulation of the pancreas or by studying short segments of small intestine. When taking into account the total pancreatic reserve capacity and total small intestinal length, however, these small decreases in digestive and absorptive ability become clinically irrelevant. This was shown in a study (which is unlikely to ever be repeated) in ~100 elderly individuals who were placed on a 100-g fat diet while in a metabolic unit for a 6-d period (Arora et al. 1989). During the last 3 d, stools were collected, and fecal fat was measured. It was found that between the age range of ~20–95 y, there was no increase in fecal fat excretion due to age, thus disproving the commonly held notion of the time that malabsorption is common in elderly persons. As mentioned, if the system is stressed (e.g., through the intake of an extremely high fat diet of ~120 g/d), elderly persons begin to show increases in fecal fat, whereas younger persons do not (Hambraeus 1972). Nevertheless, because such diets are unphysiologic, such a demonstration is not clinically pertinent.

A second principle to keep in mind when studying the bioavailability of nutrients in elderly persons is declining renal function with advancing age. This has been demonstrated in both men and women (Lindeman 1993, Sokoll et al. 1994). Renal function becomes a relevant issue to bioavailability when urinary excretion of a nutrient or nutrient metabolite is taken as a proxy measure of absorption and if the excretion of the specific nutrient or nutrient metabolite occurs primarily via the kidney. The same holds true if the blood level of a nutrient or nutrient metabolite is influenced by renal function. An example of such a nutrient is dxylose: urinary D-xylose excretion after a 25-g oral load decreases with advancing age. However, when creatinine clearances are measured, the decline in the urinary D-xylose excretion due to age can better be accounted for entirely by the decline in renal clearance, rather than by an intestinal absorptive defect (Arora et al. 1989). Similarly, measurement of vitamin B-12 bioavailability by Schilling tests or measurement of folate bioavailability by urinary excretion tests (as is done in the classic folic acid absorption test) in elderly individuals with declining kidney function might give the false impression of poor absorption, when in fact the intestinal absorption of these nutrients could be normal. Also, the metabolite homocysteine in blood is used to reflect folate status. If folate is administered to an individual with impaired renal function to correct a high serum homocysteine concentration and the concentration remains elevated, this might give the false impression that folate bioavailability is impaired (Hermann et al. 1999). Homocysteine concentrations must be interpreted in the light of renal function in the aged person and not taken as a strict measure of folate or other B vitamin status.

A third principle to keep in mind when judging the bioavailability of nutrients in elderly persons is plasma response curves after doses of fat-soluble substances may not reflect absorption but rather impaired uptake of the fat-soluble nutrient from chylomicron remnants. Vitamin A is an example of this. It was shown by Hollander and Dadufalza (1983) in rats that vitamin A absorption is increased with advancing age.

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of the animal. Similarly Krasinski et al. (1985) showed higher plasma response curves of vitamin A after a physiologic oral dose in older individuals as opposed to younger control subjects. To define whether these higher response curves were primarily a result of increased absorption versus decreased clearance, the following experiment was performed: elderly and young subjects were fed high fat, vitamin A meals, and several hours later, a unit of blood was taken for plasmapheresis. Forty-two hours later, the vitamin A–laden chylomicron remnants were reinfused into the older and young individuals in the fasting state, and plasma fall-off curves were determined. It was found that younger persons cleared vitamin A from the serum approximately twice as fast as did the elderly persons. Thus, the higher plasma response curves of the elderly persons that occurred in the original experiment of Krasinski et al. (1985) is certainly not only due to greater absorption in the small intestine as was postulated by Hollander and Dadufalza (1983) but rather to delayed clearance of the vitamin from the circulation. In the case of vitamin A, such a delayed clearance of chylomicron and chylomicron remnants causes a shift of vitamin A into other lipoprotein compartments, such as LDL. Once vitamin A in the form of retinyl esters enters these other lipoprotein particles, it is carried around in blood for a period of days (vs hours) and could conceivably act as toxin precursors. Thus, to study the true bioavailability of fat-soluble substances that are absorbed through the lymphatics, it is not sufficient to know just what the plasma response curves look like; the plasma clearance curves for the vitamin or nutrient must also be known.

**Specific problem nutrients**

The greatest change in gastrointestinal physiology affecting nutrient bioavailability that has been identified with advancing age is atrophic gastritis, which occurs in a considerable percentage of the elderly population. It was estimated that the prevalence of atrophic gastritis among older persons in Boston (using a ratio of pepsinogen I to II) is 24% in 60- to 69-y-old persons, 32% in 70- to 79-y-old persons and ~40% in ≥80-y-old persons (Krasinski et al. 1986). The prevalence of atrophic gastritis in the Midwest of the United States as diagnosed by the same pepsinogen assays and determined in the same laboratory is lower (~10% of the elderly population) (Hurwitz et al. 1997). Atrophic gastritis has been related to infection with the bacteria *Helicobacter pylori* and is not a result of normal aging; in fact, in normal aging, there is evidence that elderly persons might secrete more, rather than less, acid as is seen in atrophic gastritis (Feldman et al. 1996).

Because the overall prevalence of atrophic gastritis in elderly persons is estimated to be ~20%, this could affect the bioavailability of specific nutrients, whose absorption is pH dependent, in a considerable segment of the population. The physiologic consequences of atrophic gastritis include decreased acid-pepsin digestion in the stomach, decreased secretion of intrinsic factor (although this decrease is not sufficient to be rate limiting for vitamin B-12 absorption), bacterial overgrowth of the stomach and proximal small intestine and elevated proximal small pH. Nutrients whose absorption has been shown to be affected by low acid conditions in the stomach include folic acid, vitamin B-12, calcium, iron and beta-carotene (Russell 1986, Tang et al. 1996). Conversely, it has been shown that small intestinal bacteria in this condition may be a source of certain vitamins, including vitamin B-6 and folic acid (Camilo et al. 1996, Ribaya-Mercado et al. 1987).

**Examples of how atrophic gastritis affects nutrient bioavailability.** Active folic acid intestinal uptake has been shown to reach a maximum over a narrow pH optimum range of ~6.2–6.3 in in vitro studies (Russell et al. 1979). A value above or below this range results in diminished folate uptake by intestinal rings. Using a folate absorption test, which consists of an oral dose of tritium-labeled pteroylmethonoliglutamic acid followed by a parenteral flushing dose and a 24-h urine collection, it has been shown that elderly persons with atrophic gastritis severely malabsorb folic acid compared with normal controls (Russell et al. 1986). Moreover, this folic acid malabsorption can be corrected by administering folate along with 0.1 N hydrochloric acid to lower gastric and proximal small intestinal pH.

Atrophic gastritis may also affect the bioavailability of vitamin B-12. Dietary vitamin B-12 is associated with food proteins, which must be digested off the vitamin B-12 molecule before it is able to bind to endogenous R binders or to intrinsic factor. This digestion takes place under the influence of acid and pepsin. If stomach acid is lacking, the digestion of protein from the B12 molecule cannot take place, and the binding of vitamin B-12 to intrinsic factor further down in the small intestine, therefore, also cannot take place. King et al. (1979) described a group of five individuals with gastrointestinal disease who had diminished absorption of vitamin B-12 when the vitamin was bound to chicken serum protein. This malabsorption could not be corrected by giving intrinsic factor along with the protein-bound vitamin B-12. However, the administration of acid with the protein-bound vitamin B-12 increased its absorption to within the normal range in two individuals, and the administration of acid along with pepsin (with or without intrinsic factor) further increased the absorption in most of the others. It is interesting that all five of these individuals were able to normally absorb crystalline vitamin B-12. It was subsequently shown that the malabsorption of protein-bound vitamin B-12 in individuals with atrophic gastritis can also be reversed by lowering bacteria in the proximal small intestine through the use of antibiotics (Suter et al. 1991). From these combined studies, it appears that impaired digestion, and therefore the release of free vitamin B-12 into the lumen of the small bowel, takes place in atrophic gastritis due to low acid secretion. The low intraluminal concentrations of free vitamin B-12, which occur after the feeding of food-bound B12, allow for bacterial uptake of the free vitamin. However, crystalline vitamin B-12 in a Schilling test can overwhelm the bacterial binding capacity. Thus, this is an example of a vitamin preparation that is clearly superior to that of the food-bound vitamin in terms of bioavailability. That is, persons with atrophic gastritis should consume oral vitamin B-12 supplements or food that has been artificially fortified with vitamin B-12 to ensure normal vitamin B-12 nutriture.

Iron and calcium are other nutrients whose bioavailability is affected by atrophic gastritis. Decreased iron absorption has been reported in old age, but many studies were not well controlled for iron status or for the presence of gastrointestinal disease. It has been demonstrated that the absorption of ferric iron is diminished in achlorhydric subjects (Choudhury and Williams 1959). Acid serves to keep the ferric iron in solution until it reaches the absorptive sites of the duodenal mucosa. Ferric iron is insoluble above pH 5, although ferrous iron and heme iron remain in solution at neutral or slightly alkaline pH values. Substances that ligand ferric iron, such as ascorbate, increase the absorption of ferric iron at a neutral or slightly alkaline pH range. However, chelation must occur when the iron is in solution, that is, when the iron is in acid milieu. Thus, acidity is needed for the chelation of ferric iron to take place, which will then be kept in solution at the higher pH of the proximal small intestine, so iron will be available for absorption. Heme iron does not appear to be affected by lack
of acid and thus is normally absorbed in individuals with atrophic gastritis. Elderly persons show reduced absorption of calcium, in general, which is related to age-related changes in vitamin D metabolism. For example, decreased skin synthesis, decreased vitamin D absorption, decreased vitamin D receptors in the intestinal epithelial cell and impaired conversion of 25-hydroxy vitamin D to the active hormonal form 1,25-dihydroxy vitamin D have all been demonstrated (Barragy et al. 1978, Ebeling et al. 1992, Holick et al. 1989, Tsai et al. 1984). In addition, elderly individuals show a reduced ability to adapt to low calcium diets by increasing the efficiency of calcium absorption, whereas younger individuals are able to make such an adaptation (Ireland and Dordtran 1973). As previously mentioned, atrophic gastritis can also affect calcium absorption. Calcium carbonate reacts with hydrochloric acid to form soluble calcium chloride, which is subsequently absorbed in the proximal small bowel. In atrophic gastritis due to the absence of acid, calcium may not be solubilized or absorbed.

Finally, it was recently shown by Tang et al. (1996) that gastric acidity increases a blood response to a beta-carotene dose, thereby implicating a negative effect of atrophic gastritis with reduced gastric acid levels on beta-carotene absorption.

In considering bioavailability, one is talking not only about absorption but also about activation and metabolism of the nutrient in the body. This should also be considered in elderly subjects, although very little is known about this for most nutrients. For vitamin D, as has been already mentioned, there is impaired conversion in elderly persons of 25-dihydroxy vitamin D to 1,25-dihydroxy vitamin D after parathyroid hormone stimulation. Elderly persons have also been shown to have an increased vitamin B-6 requirement compared with younger persons, although the reason for this is obscure (Ribaya-Mercado et al. 1991). The higher vitamin B-6 requirement does not appear to be due to a malabsorptive problem, but rather there may be a problem in metabolism of the vitamin after absorption has occurred.

Research agenda for elderly persons

In view of these special considerations mentioned here, the following is a proposed research agenda for the study of the bioavailability of nutrients and other bioactive components of dietary supplements in elderly persons:

For all fat-soluble substances, to determine bioavailability not only in terms of absorption but also in terms of clearance from the circulation into peripheral tissues. Do all fat-soluble substances that are absorbed in chylomicrons act similar to vitamin A?

To study the bioactivation and metabolism of nutrients in the elderly. There are changes in vitamin D metabolism with aging, but it is not clear whether there are similar changes in the conversion of provitamin A carotenoids to vitamin A or for the activation of vitamin B-6, as mentioned here. Such knowledge may determine the form of a nutrient that is in a supplement.

To use stable isotope techniques to determine the bioavailability of nutrients and other bioactive components. This is a highly useful technique that yields more exact results than the techniques that are presently available to assess bioavailability (e.g., plasma response curves).

To broaden study from that of the known vitamins and minerals (for which we have at least some knowledge) to that of the bioavailability and metabolism of other bioactive substances, such as isoflavones, polyphenols and carotenoids, other than B-carotene. These former two are of particular interest because of their high antioxidant capacity and because they are consumed in relatively large amounts. For example, a normal diet contains ~200 mg polyphenols compared with 3–5 μg beta-carotene. More attention should be paid to these food components than in the past. Also, it is important to study these other bioactive components, because aging persons might be more prone to supplement themselves with these substances in large amounts to “stave off” the aging process.

To better define drug-nutrient interactions, of which now we know very little. The focus should be on drugs that are commonly taken by older persons.

LITERATURE CITED


