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Biotin bioavailability and estimated average requirement: why bother?[1,2]

Hamid M Said

Frank, symptomatic biotin deficiency probably occurs rarely. The only well-documented cases have occurred in association with total or near total intravenous feeding without biotin supplementation, chronic egg white feeding, or inborn errors of metabolism that lead to biotin wasting (1). A single case that does not fit any of the 3 established associations is that of an infant fed a rice-based formula that was presumably very low in biotin (2).

However, there are lines of investigation suggesting that the virtual absence of spontaneous, overt biotin deficiency does not imply optimal biotin nutritional status in all normal circumstances. Of particular concern is pregnancy. Many previous studies have shown that biotin deficiency is teratogenic in several animal species, including mice, hamsters, chickens, and turkeys. A recent study (3) revealed a high incidence of skeletal malformations, including a >50% incidence of cleft palate in fetuses of biotin-deficient mouse dams who showed no physical evidence of biotin deficiency. Moreover, neither reproductive efficiency nor fetal weight gain was affected.

Although conclusions of previous studies of biotin status during pregnancy disagreed (4–6), recent studies suggest that marginal biotin status may be common during normal pregnancy. Two well-validated indexes of biotin nutritional status, decreased urinary excretion of biotin and increased urinary excretion of 3-hydroxyisovaleric acid (3-HIA), which reflects decreased tissue activity of the biotin-dependent enzyme β-methylcrotonyl-CoA carboxylase, were then used to assess biotin status in 2 studies of normal human gestation. The initial study used a cross-sectional design. The study detected increased 3-HIA excretion both early and late in pregnancy, but biotin excretion increased rather than decreased late in pregnancy (7). A second study followed a cohort of women longitudinally from early to late pregnancy and, thus, allowed for more rigorous prevention of inadvertent biotin supplementation. This longitudinal study also detected increased 3-HIA excretion early and late in pregnancy; moreover, urinary biotin excretion decreased from early to late in pregnancy (8). Accelerated biotransformation of biotin to inactive metabolites was observed in both of these studies and may have contributed to the development of marginal biotin status. The possibility that biotin status may often be marginal in the first trimester of pregnancy is of particular interest because critical stages of organogenesis occur in the first trimester and because of the well-established role of supplementation of the water-soluble vitamin folic acid in prevention of neural tube defects (9).

Despite increasing interest in biotin nutriture, considerable basic information concerning biotin bioavailability and nutritional status remains unknown. The paper by Zempleni and Mock (10) in this issue makes a significant contribution to information concerning bioavailability. Biotin was administered orally in pharmacologic amounts (2.1, 8.2, or 89.1 μmol) to 6 healthy adults. The increased urinary excretion of biotin and biotin metabolites in the subsequent 24 h was quantitated specifically for biotin and each metabolite. Bioavailability was calculated relative to a similar sum of biotin and biotin metabolites excreted after a midrange dose of biotin (18.4 μmol) was administered intravenously. Bioavailability of the 2 largest oral doses was ≈100%. For unexplained reasons, the apparent recovery of the smallest dose yielded a bioavailability of ≈200%. Notwithstanding the failure to explain an apparent bioavailability >100%, the study of Zempleni and Mock adds significantly to our understanding of biotin bioavailability because advanced analytic techniques were used. Biotin and biotin metabolites were measured discretely and accurately by using HPLC to separate biotin and its metabolites, followed by quantitation with an avidin-binding assay using standard curves for biotin and each metabolite. Previous studies also measured increased urinary excretion of biotin after oral administration; bioavailabilities were calculated as a ratio of biotin excreted in the urine to the dose administered. Microbial assays that do not detect most biotin metabolites (11) or avidin-binding assays that do not take into account the smaller binding affinities of biotin metabolites for avidin (12) have also been used to quantitate biotin. Because biotin metabolites account for approximately one-half of the sum of biotin plus metabolites on a molar basis in urine, previous studies are likely to have significantly underestimated the bioavailability of biotin. Moreover, previous studies did not use an intravenous dose of biotin as a reference. Researchers in previous studies recognized that the measured bioavailabilities (24–58%) were probably minimum estimates.

Pharmacologic doses of biotin are commonly given to treat biotin-dependent, inborn errors of metabolism. Thus, results of the study by Zempleni and Mock are directly useful for the small group of patients in whom megadose biotin therapy is justified.

[1] From the Veterans Administration Medical Center, Long Beach, CA, and the University of California School of Medicine, Irvine.

[2] Address correspondence to HM Said, VA Medical Center-151, Long Beach, CA 90822. E-mail: hmsaid@uci.edu.

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Moreover, the finding of high bioavailability of biotin at pharmacologic doses provides at least some basis for predicting that bioavailability will also be high at lower doses. Unfortunately, the desire to avoid the administration of radioactive biotin and a lack of both stable isotope–labeled biotin and a published mass spectrometric method for quantitation of stable isotope–labeled biotin in urine currently prevent bioavailability studies at tracer and physiologic doses.

To determine an estimated average requirement and a recommended daily intake for biotin, the biotin content and bioavailability of biotin in common foods should be determined. Current knowledge is limited in this area. Human milk is the only food for which the relative contribution of biotin compared with that of biotin metabolites has been determined (13). Biotin metabolite content exceeded biotin content in early and transitional milk; in mature milk, biotin accounted for ≈75% of the total. Thus, biotin and biotin metabolites should probably be quantitated separately and specifically. In addition, it is likely that a substantial portion of the biotin in many foodstuffs is protein bound (1). Data assessing the completeness of release of biotin and the degree of destruction of biotin in the process of release for assay preparation are largely absent. For human milk, acid hydrolysis methods used for several studies destroyed between 12% and 37% of biotin (14). Such destruction would likely lead to an underestimation of the true biotin content of the food.

In summary, clinical observations made with newly validated measures of biotin status have recently focused attention on biotin nutriture; however, important information in several basic areas is currently unavailable. The paper by Zempleni and Mock provides an example in which the application of more advanced analytic techniques has revealed that biotin administered orally is almost completely bioavailable, at least in large doses.

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