



Biotin: the forgotten vitamin^{1,2}

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Biotin, an essential micronutrient for all mammals, is a member of the B complex group of vitamins. Biotin was discovered in nutritional experiments that revealed a factor in many foodstuffs that was capable of curing the scaly dermatitis, hair loss, and neurologic signs induced in rats fed dried egg whites. Avidin, a glycoprotein found in egg whites, binds biotin very specifically and tightly ($K_a = 10^{15}$ mol/L) (1, 2). From an evolutionary standpoint, avidin probably serves as a bacteriostat in egg whites because it is resistant to a broad range of bacterial proteases in both the free and biotin-bound forms. Because it is resistant to pancreatic proteases, dietary avidin binds to dietary biotin (and probably to any biotin from intestinal microbes) and prevents its absorption. Biotin is synthesized by the normal microflora of the large intestine and is partly absorbed by colonocytes (3). However, the contribution of this source of biotin to overall host nutrition is not known (2, 4). Cooking denatures avidin, rendering it susceptible to digestion and unable to interfere with the intestinal absorption of biotin.

The fact that humans have a requirement for biotin has been most clearly shown in 2 situations that result in biotin deficiency: 1) prolonged consumption of raw egg whites and 2) parenteral nutrition without biotin supplementation in patients with short-gut syndrome (2). It could be argued that the biotin supply from gut microbes was also interrupted in each of these situations. One might infer that biotin deficiency is not a concern except in rare circumstances because sufficient biotin may be supplied by gut microbes. However, frank biotin deficiency was also found in 2 infants fed a formula without biotin (5, 6). Additionally, persons with a genetic deficiency of biotinidase become biotin deficient (7). In this case, biotin deficiency probably results from a combination of impaired intestinal absorption of biotin because of the failure of biotinidase to release biotin bound covalently to dietary protein, inefficient salvage of biotin during cellular protein turnover because of the failure of biotinidase to release biotin from carboxylases, and increased renal loss of biocytin (7, 8). The phenotypes of biotinidase deficiency and biotin deficiency are quite similar but not identical. The common pathogenic mechanism probably involves decreased activities of the biotin-dependent carboxylases but may also involve other problems with biotinylation, such as those involving histones.

The biotin requirements for normal persons and for persons in special clinical circumstances are not known. Safe and adequate intakes have been suggested (9, 10). These gaps in our fundamental knowledge of human nutrition have arisen from at least 2 sources: 1) a lack of analytic tools to quantitate biotin in body fluids and the metabolic disturbances caused by biotin defi-

ciency and 2) a lack of experimental validation of putative indexes of biotin status (11, 12). These needs have been partially addressed in the past 10 y. Mock and colleagues (13) developed and applied a sensitive (≈ 2 parts per trillion) and chemically specific assay for biotin. The assay combines HPLC with an avidin binding assay. Using this assay, they detected substantial amounts of biotin metabolites in human urine and plasma (14). In studies in which marginal, asymptomatic biotin deficiency was induced experimentally in healthy adults by the feeding of egg whites, decreased urinary excretion of biotin was found to be an early and sensitive indicator of biotin deficiency.

Biotin is a covalently bound prosthetic group for 5 mammalian carboxylases, including methylcrotonyl-CoA carboxylase. When the activity of methylcrotonyl-CoA carboxylase is decreased, its substrate, 3-methylcrotonyl-CoA, is shunted to an alternate metabolic pathway, producing 3-hydroxyisovaleric acid (3-HIA), which is then excreted in increased quantities in urine. Using unlabeled and uniformly deuterated 3-HIA as internal and external standards, respectively, Mock and colleagues (13) developed and applied a highly accurate gas chromatography–mass spectrometry method for quantitating the urinary excretion of this organic acid. An elevated urinary concentration of 3-HIA was found to be an early and sensitive indicator of biotin deficiency.

Maternal and fetal vitamin status in general and biotin status in particular have been areas of interest and concern for many decades. Although frank biotin deficiency has never been documented in normal human gestation, biotin deficiency is a potent teratogenic event in some mammalian species (15–17). Moreover, weak human placental transport of biotin (18) may allow maternal biotin deficiency to cause fetal biotin deficiency.

As pointed out by Mock et al (19) in this issue of the Journal, the conclusions of earlier studies on maternal biotin status have conflicted (20–22). However, studies incorporating these validated indexes provide evidence that marginal, asymptomatic biotin deficiency is a common occurrence in normal human pregnancy (23, 24). In those studies, assertions concerning decreased biotin status depended importantly on the presence of increased urinary excretion of 3-HIA. In most of these women, the urinary excretion of biotin was normal in early pregnancy and decreased

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to abnormal values in late pregnancy in only a few of the women. Mock et al questioned whether the observed increase in 3-HIA excretion might have simply been the result of pregnancy because of an effect on protein turnover, amino acid metabolism, or renal excretion of organic acids. The study by Mock et al provides strong evidence that biotin supplementation decreases 3-HIA excretion in pregnant women whose urinary excretion of 3-HIA is elevated. This result is consistent with Mock et al's hypothesis that increased urinary excretion of 3-HIA does indeed reflect marginal biotin deficiency.

Additional plausibility for their interpretation comes from the demonstration of a mechanism for biotin deficiency. Studies of biotin catabolism in pregnancy indicate that the urinary excretions of bisnorbiotin, biotin sulfoxide, and other inactive biotin metabolites are \approx 4-fold greater than the excretion of biotin (23, 24). Studies of accelerated biotin catabolism in rats detected a 4-fold acceleration of biotin catabolism induced by steroids (25). In pregnant women, the increased rates of catabolism of biotin in comparison with its intake suggest that degradation could be a major cause of biotin deficiency.

I concur with the authors that the findings of their study should not be generalized to current nutritional practice in pregnancy. The findings reported by Mock et al do not justify widespread biotin supplementation during pregnancy. Ideally, the incidence of marginal biotin deficiency should be assessed by a complementary index of biotin status that does not depend on maternal renal function, if such an index can be discovered and validated. Moreover, a causal link between maternal biotin deficiency and deleterious effects on the fetus or mother must be established. Finally, both the appropriate dosage of biotin and the timing of the dosage with respect to conception required for therapeutic efficacy must be determined. 

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