Vitamin B-12[1]

Vitamin B-12 is a cofactor for 2 enzymes. In the cytoplasm, methionine synthase requires vitamin B-12 in the form of methylcobalamin and catalyzes the conversion of homocysteine to methionine by transfer of a methyl group from methyltetrahydrofolate. This enzyme links the methylation pathway through synthesis of the methyl donor S-adenosyl methionine and the pathway in which purine and pyrimidine are synthesized via generation of tetrahydrofolate. In the form of 5′-deoxyadenosylcobalamin, vitamin B-12 is also required for the mitochondrial enzyme methylmalonyl CoA mutase, which converts methylmalonyl CoA to succinyl CoA, a step in the oxidation of odd-chain fatty acids and catabolism of ketogenic amino acids. Thus, vitamin B-12 is important for DNA synthesis, regenerating methionine for protein synthesis and methylation, and preventing homocysteine accumulation (1).

Deficiencies: Serum (or plasma) vitamin B-12 concentration is the most frequently used biomarker of status with values <150 pmol/L (<200 pg/mL) indicating deficiency, and 150–221 pmol/L (200–300 pg/mL) indicating depletion. Holotranscobalamin may be a more sensitive indicator of depletion than serum vitamin B-12 in some conditions (e.g., after intestinal radiation therapy for cancer and in HIV/AIDS), but the usual cutoff of 30 pmol/L (40 pg/mL) often estimates a similar population prevalence of deficiency as serum vitamin B-12. Holotranscobalamin is the metabolically active transport form of the vitamin, so there is interest in whether it is more sensitive for detecting the adverse effects of deficiency on function. Elevated serum or urinary methylmalonic acid is the most specific indicator of vitamin B-12 deficiency, but its analysis is usually expensive and more difficult than serum vitamin B-12, and serum creatinine must be measured to confirm normal renal function. Plasma total homocysteine is a relatively sensitive indicator of vitamin B-12 deficiency, but it is not specific; it is also increased in folate, riboflavin, and vitamin B-6 deficiencies and in conditions such as hypothyroidism and kidney disease. Relatively severe vitamin B-12 deficiency impairs red blood cell synthesis (megaloblastic anemia due to abnormal DNA synthesis) and neurological function (demyelination of nerves in part due to abnormal methylation, leading to peripheral neuropathy, dementia, poor cognitive performance, and depression). Some neurological effects can be permanent, especially after 1 y. Deficiency or depletion is also associated with increased risk of neural tube defects, bone loss, and inflammation. Breast-fed infants born to mothers who are strictly vegetarian are at risk of permanent developmental delays because they have low vitamin B-12 stores at birth followed by low concentrations of the vitamin in breast milk (2).

Diet recommendations: The recommended dietary allowance (in μg/d) is 0.4 for the first 6 mo of life and 0.5 for 6–12 mo, 0.9 for 1–3 y, 1.2 for 4–8 y, 1.8 for 9–13 y, and 2.4 for 14 y through old age. In pregnancy, 2.6 μg is recommended, and in lactation, 2.8 μg (3). Based on an estimated 10–30% prevalence of malabsorption of vitamin B-12 from food in the elderly, after age 50 y it advised that most of the requirement be met through fortified foods or a supplement because crystalline vitamin B-12 is likely to be better absorbed.

Food sources: Vitamin B-12 is found naturally only in animal source foods such as dairy products, meat, eggs, fish, and shellfish. These contain 1–10 μg/100 g wet weight. Liver and kidney contain >10 μg/100 g, but the efficiency of vitamin B-12 absorption decreases markedly when a meal contains more than ~2 μg, so the effective content of these sources becomes only ~20% of that listed in food composition tables. Lacto-ovo vegetarians, who avoid meat in their diet, have lower intakes and serum concentrations of the vitamin than omnivores, as does a high proportion of the population in the world that has limited access to animal source foods. Vitamin B-12 fortification of flour is increasingly recommended in developing countries, but more efficacy and effectiveness trials testing different doses are needed. People who strictly avoid all animal source foods will definitely become deficient unless they take supplements or fortified foods. Fortified foods, such as breakfast cereals, often supply an important proportion of the usually daily intake.

Clinical uses: The 2 best known clinical conditions that require vitamin B-12 therapy are pernicious anemia and vitamin B-12 deficiency in the elderly. Pernicious anemia is an autoimmune condition in which destruction of gastric parietal cells leads to loss of the

 Adv. Nutr. 3: 54–55, 2012; doi:10.3945/an.111.001370.

intrinsic factor required for the active absorption of the vitamin. It is a relatively rare condition, affecting only 2–3% of the population. Vitamin B-12 deficiency in the elderly is more common and usually diagnosed from low serum vitamin B-12 concentrations or, less often, from signs of neuropathy or megaloblastic anemia. Both conditions can be managed with high doses of intramuscular (500–1000 μg, once or twice weekly for 6 wk, then once per month) or oral (500–1000 μg/d) cyanocobalamin, hydroxocobalamin, or methylcobalamin. Supplemental vitamin B-12 is also often used to prevent deficiency after partial or total gastrectomy, ileal resection, prolonged use of proton pump inhibitors, and other intestinal or drug-related conditions that impair vitamin B-12 absorption or metabolism.

Toxicity: No toxic effects of vitamin B-12 have been identified, even when it is administered intramuscularly at 300–3000 times the recommended dietary allowance. For this reason, no upper tolerable level for the vitamin has been established.

Recent research: There is interest in whether high folic acid intake, which can occur when fortified foods and supplements are both consumed, exacerbates the effects of vitamin B-12 deficiency on neurological and cognitive function and anemia (4), but more research is needed to confirm the limited data available. The causes of the increased prevalence of deficiency in the elderly are uncertain and require more study in population groups. Several ongoing longitudinal studies are evaluating the effects of vitamin B-12 supplementation on cognitive and neurophysiological function in the elderly to confirm whether supplementation can prevent the cognitive and neurological decline with aging. Information is gradually accumulating about the adverse effects of B-12 deficiency and benefits of supplementation in populations with a chronically low intake throughout their life span, including pregnancy outcomes such as low birth weight, child development, and school performance. The value of measuring holotranscobalamin rather than or in combination with serum vitamin B-12 is being tested (5). The possible long-term consequences of the epigenetic effects of vitamin B-12 deficiency in pregnancy are under investigation. Single nucleotide polymorphisms in proteins involved in vitamin B-12 metabolism, including the transport proteins transcobalamin 1 and 2, cubulin, FUT2, intrinsic factor, and methionine synthase are being studied for their association with vitamin B-12 absorption, metabolism, and function (6). New tests to detect vitamin B-12 malabsorption using ^{14}C-labeled vitamin B-12 may replace the Schilling test, which is now rarely used. The gut microbiome appears to degrade unabsorbed vitamin B-12, but how it affects absorption and degradation of the vitamin is not yet clear. There is some evidence that vitamin B-12 deficiency might increase the inflammatory cytokine TNF-α resulting in neurodegeneration (7). Dietary intake recommendations need to be revised for lactating women and infants based on the recent recognition that older methods of analyzing vitamin B-12 in human milk were invalid (8). More information is needed on the intake needed to normalize vitamin B-12 status biomarkers in relation to the changing efficiency of vitamin B-12 absorption across the usual range of intake from food.

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[1]Author disclosure: Lindsay H. Allen, no conflicts of interest.

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Acknowledgments

The sole author had responsibility for all parts of the manuscript.

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