9

Vitamin B_{12}

SUMMARY

Vitamin B_{12} (cobalamin) functions as a coenzyme for a critical methyl transfer reaction that converts homocysteine to methionine and for a separate reaction that converts L-methylmalonyl-coenzyme A (CoA) to succinyl-CoA. The Recommended Dietary Allowance (RDA) for vitamin B_{12} is based on the amount needed for the maintenance of hematological status and normal serum vitamin B_{12} values. An assumed absorption of 50 percent is included in the recommended intake. The RDA for adults is 2.4 µg/day of vitamin B_{12}. Because 10 to 30 percent of older people may be unable to absorb naturally occurring vitamin B_{12}, it is advisable for those older than 50 years to meet their RDA mainly by consuming foods fortified with vitamin B_{12} or a vitamin B_{12}-containing supplement. Individuals with vitamin B_{12} deficiency caused by a lack of intrinsic factor require medical treatment. The median intake of vitamin B_{12} from food in the United States was estimated to be approximately 5 µg/day for men and 3.5 µg/day for women. The ninety-fifth percentile of vitamin B_{12} intake from both food and supplements was approximately 27 µg/day. In one Canadian province the mean dietary intake was estimated to be approximately 7 µg/day for men and 4 µg/day for women. There is not sufficient scientific evidence to set a Tolerable Upper Intake Level (UL) for vitamin B_{12} at this time.

BACKGROUND INFORMATION

Cobalamin is the general term used to describe a group of cobalt-containing compounds (corrinoids) that have a particular structure that contains the sugar ribose, phosphate, and a base (5, 6-dimethyl benzimidazole) attached to the corrin ring. Vitamin B_{12} can be converted to either of the two cobalamin coenzymes that are active in human metabolism: methylcobalamin and 5-deoxyadenosylcobalamin. Although the preferred scientific use of the term *vitamin B_{12}* is usually restricted to cyanocobalamin, in this report, B_{12} will refer to all potentially biologically active cobalamins.

In the United States, cyanocobalamin is the only commercially available B_{12} preparation used in supplements and pharmaceuticals. It is also the principal form used in Canada (B. A. Cooper, Department of Hematology, Stanford University, personal communication, 1997). Another form, hydroxocobalamin, has been used in some studies of B_{12}. Compared with hydroxocobalamin, cyanocobalamin binds to serum proteins less well and is excreted more rapidly (Tudhope et al., 1967).

Function

B_{12} is a cofactor for two enzymes: methionine synthase and L-methylmalonyl-CoA mutase. Methionine synthase requires methylcobalamin as a cofactor for the methyl transfer from methyltetrahydrofolate to homocysteine to form methionine and tetrahydrofolate. L-Methymalonyl-CoA mutase requires adenosylcobalamin to convert L-methymalonyl-CoA to succinyl-CoA in an isomerization reaction. In B_{12} deficiency, folate may accumulate in the serum as a result of slowing of the B_{12}-dependent methyltransferase. An adequate supply of B_{12} is essential for normal blood formation and neurological function.

Physiology of Absorption, Metabolism, Storage, and Excretion

Small amounts of B_{12} are absorbed via an active process that requires an intact stomach, intrinsic factor (a glycoprotein that the parietal cells of the stomach secrete after being stimulated by food), pancreatic sufficiency, and a normally functioning terminal ileum. In the stomach, food-bound B_{12} is dissociated from proteins in the presence of acid and pepsin. The released B_{12} then binds to R proteins (haptocorrins) secreted by the salivary glands and the gastric mucosa. In the small intestine, pancreatic proteases partially de-

grade the R proteins, releasing B_{12} to bind with intrinsic factor. The resulting complex of intrinsic factor and B_{12} attaches to specific receptors in the ileal mucosa; after internalization of the complex, B_{12} enters the enterocyte. Approximately 3 to 4 hours later, B_{12} enters the circulation. All circulating B_{12} is bound to the plasma binding proteins—transcobalamin I, II, or III (TCI, TCII, or TCIII). Although TCI binds approximately 80 percent of the B_{12} carried in the blood, TCII is the form that delivers B_{12} to the tissues through specific receptors for TCII (Hall and Finkler, 1966; Seetharam and Alpers, 1982). The liver takes up approximately 50 percent of the B_{12} and the remainder is transported to other tissues.

If there is a lack of intrinsic factor (as is the case in the condition called pernicious anemia), malabsorption of B_{12} results; if this is untreated, potentially irreversible neurological damage and life-threatening anemia develop.

The average B_{12} content of liver tissue is approximately 1.0 µg/g of tissue in healthy adults (Kato et al., 1959; Stahlberg et al., 1967). Estimates of the average total-body B_{12} pool in adults range from 0.6 (Adams et al., 1972) to 3.9 mg (Grasbeck et al., 1958), but most estimates are between 2 and 3 mg (Adams, 1962; Adams et al., 1970; Heinrich, 1964; Reizenstein et al., 1966). The highest estimate found for an individual's total body B_{12} store was 11.1 mg (Grasbeck et al., 1958). Excretion of B_{12} is proportional to stores (see "Excretion").

Absorption

Studies to measure the actual absorption of B_{12} involve whole-body counting of radiolabeled B_{12}, counting of radiolabeled B_{12} in the stool, or both. No data are available on whether B_{12} absorption varies with B_{12} status, but fractional absorption decreases as the oral dose is increased (Chanarin, 1979). Total absorption increases with increasing intake. Adams and colleagues (1971) measured fractional absorption of radiolabeled cyanocobalamin and reported that nearly 50 percent was retained at a 1-µg dose, 20 percent at a 5-µg dose, and just over 5 percent at a 25-µg dose. The second of two doses of B_{12} given 4 to 6 hours apart is absorbed as well as the first (Heyssel et al., 1966). When large doses of crystalline B_{12} are ingested, up to approximately 1 percent of the dose may be absorbed by mass action even in the absence of intrinsic factor (Berlin et al., 1968; Doscherholmen and Hagen, 1957).

Absorption from Food. The approximate percentage absorption of B_{12} from a few foods is presented in Table 9-1. These values apply to normal, healthy adults. No studies were found on the absorption of B_{12} from dairy foods or from red meat other than mutton and liver. The absorption efficiency of B_{12} from liver reportedly was low because of its high B_{12} content. Although evidence indicates that a B_{12} content of 1.5 to 2.5 µg/meal saturates ileal receptors and thus limits further absorption (Scott, 1997), absorption of as much as 7 µg in one subject (18 percent) was reported from a serving of liver paste that contained 38 µg of B_{12} (average absorption was 4.1 µg or 11 percent) (Heyssel et al., 1966).

Assumptions Used in this Report. Because of the lack of data on dairy foods and most forms of red meat and fish, a conservative adjustment for the bioavailability of naturally occurring B_{12} is used in this report. In particular, it is assumed that 50 percent of dietary B_{12} is absorbed by healthy adults with normal gastric function. A smaller fractional absorption would apply, however, if a person consumed a large portion of foods rich in B_{12}. Different levels of absorption are assumed under various conditions, as shown in Table 9-2. Crystalline B_{12} appears in the diet only in foods that have been fortified with B_{12}, such as breakfast cereals and liquid meal replacements.

Enterohepatic Circulation

B_{12} is continually secreted in the bile. In healthy individuals most of this B_{12} is reabsorbed and available for metabolic functions. El Kholty et al. (1991) demonstrated that the secretion of B_{12} into the bile averaged 1.0 ± 0.44 nmol/day (1.4 µg/day) in eight cholecystectomized patients, and this represented 55 percent of total corrinoids. If approximately 50 percent of this B_{12} is assumed to be

TABLE 9-1 Percentage Absorption of Vitamin B_{12} from Foods by Healthy Adults

Reference	Food	Absorption (%)
Heyssel et al., 1966	Mutton	65
Heyssel et al., 1966	Liver	11
Doscherholmen et al., 1975	Eggs	24–36
Doscherholmen et al., 1978	Chicken	60
Doscherholmen et al., 1981	Trout	25–47

TABLE 9-2 Assumed Vitamin B_{12} Absorption under Different Conditions

Form of Vitamin B_{12}	Normal Gastric Function (%)	Pernicious Anemia[a] (%)
Naturally occurring[b]	50	0
Crystalline, low dose (< 5 μg)[b]	60	0
Crystalline, high dose (≥ 500 μg) with water[c]	1	1
Crystalline, high dose with food[c]	0.5	≤ 0.5

[a] A disorder in which lack of intrinsic factor severely limits the absorption of vitamin B_{12}.
[b] Heyssel et al. (1966).
[c] Berlin et al. (1968).

reabsorbed, the average loss of biliary B_{12} in the stool would be 0.5 nmol/day (0.7 μg/day). Research with baboons (Green et al., 1982) suggests that the form of B_{12} present in bile may be absorbed more readily than is cyanocobalamin, but the absorption of both forms was enhanced by intrinsic factor. Both Green and colleagues (1982) and Teo and coworkers (1980) reported data suggesting that bile enhances B_{12} absorption. However, in the absence of intrinsic factor, essentially all the B_{12} from the bile is excreted in the stool rather than recirculated. Thus, B_{12} deficiency develops more rapidly in individuals who have no intrinsic factor or who malabsorb B_{12} for other reasons than it does in those who become complete vegetarians and thus ingest no B_{12}.

Excretion

If the circulating B_{12} exceeds the B_{12} binding capacity of the blood, the excess is excreted in the urine. This typically occurs only after injection of B_{12}. The highest losses of B_{12} ordinarily occur through the feces. Sources of fecal B_{12} include unabsorbed B_{12} from food or bile, desquamated cells, gastric and intestinal secretions, and B_{12} synthesized by bacteria in the colon. Other losses occur through the skin and metabolic reactions. Fecal (Reizenstein, 1959) and urinary losses (Adams, 1970; Heinrich, 1964; Mollin and Ross, 1952) decrease when B_{12} stores decrease. Various studies have indicated losses of 0.1 to 0.2 percent of the B_{12} pool per day (Amin et al., 1980; Boddy and Adams, 1972; Bozian et al., 1963; Heinrich, 1964; Heyssel et al., 1966; Reizenstein et al., 1966) regardless of the size of the store, with the 0.2 percent value generally applicable to those with pernicious anemia.

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