Update on Vitamin B_{12} Deficiency

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Vitamin B_{12} (cobalamin) deficiency is a common cause of megaloblastic anemia, a variety of neuropsychiatric symptoms, and elevated serum homocysteine levels, especially in older persons. There are a number of risk factors for vitamin B_{12} deficiency, including prolonged use of metformin and proton pump inhibitors. No major medical organizations, including the U.S. Preventive Services Task Force, have published guidelines on screening asymptomatic or low-risk adults for vitamin B_{12} deficiency, but high-risk patients, such as those with malabsorptive disorders, may warrant screening. The initial laboratory assessment of a patient with suspected vitamin B_{12} deficiency should include a complete blood count and a serum vitamin B_{12} level. Measurements of serum vitamin B_{12} may not reliably detect deficiency, and measurement of serum homocysteine and/or methylmalonic acid should be used to confirm deficiency in asymptomatic high-risk patients with low normal levels of vitamin B_{12}. Oral administration of high-dose vitamin B_{12} (1 to 2 mg daily) is as effective as intramuscular administration in correcting the deficiency, regardless of etiology. Because crystalline formulations are better absorbed than naturally occurring vitamin B_{12}, patients older than 50 years and strict vegetarians should consume foods fortified with vitamin B_{12} and vitamin B_{12} supplements, rather than attempting to get vitamin B_{12} strictly from dietary sources. Administration of vitamin B_{12} to patients with elevated serum homocysteine levels has not been shown to reduce cardiovascular outcomes in high-risk patients or alter the cognitive decline of patients with mild to moderate Alzheimer disease. (***Am Fam Physician*. 2011;83(12):1425-1430.**

▶ **Patient information:** A handout on this topic is available at http://familydoctor.org/765.

Vitamin B_{12} (cobalamin) is a water-soluble vitamin that is crucial to normal neurologic function, red blood cell production, and DNA synthesis. Vitamin B_{12} is essential for three enzymatic processes: the conversion of homocysteine to methionine; the conversion of methylmalonic acid to succinyl coenzyme A; and the conversion of 5-methyltetrahydrofolate to tetrahydrofolate, a process necessary for DNA synthesis and red blood cell production.[1] It cannot be manufactured by humans and must be regularly obtained from the ingestion of animal proteins or fortified cereal products. Gastric acid liberates vitamin B_{12} from animal proteins, after which it combines with intrinsic factor produced by gastric parietal cells and is absorbed in the terminal ileum.

Pernicious anemia, which is characterized by an autoimmune-mediated chronic atrophic gastritis, is a classically described cause of vitamin B_{12} deficiency[2]; other common causes include postsurgical malabsorption, dietary deficiencies, and vitamin B_{12} malabsorption from food.[3] Because of extensive hepatic stores of vitamin B_{12}, there may be a five- to 10-year delay between the onset of deficiency and the appearance of clinical symptoms.[4]

In asymptomatic patients with low-normal levels of vitamin B_{12} (200 to 350 pg per mL [147.56 to 258.23 pmol per L]), elevated levels of the precursor compounds homocysteine and methylmalonic acid may prompt a decision to supplement patients with vitamin B_{12}.[5]

The true prevalence of vitamin B_{12} deficiency is difficult to estimate because reports are based on values that vary because of inclusion criteria and individual laboratory methodology. In 1994, the Framingham Heart Study reported the prevalence of vitamin B_{12} deficiency, as defined by a serum vitamin B_{12} level less than 200 pg per mL and elevated levels of serum homocysteine, methylmalonic acid, or both, to be 12 percent among 548 community-dwelling older patients.[6] However, most deficient patients did not have hematologic manifestations, and neurologic manifestations were not assessed. According to unpublished data from the National Health and Nutrition Examination Survey, 3.2 percent of U.S. adults older than 50 years are estimated to have a serum vitamin B_{12} level less than 200 pg per mL.[1] Risk factors for vitamin B_{12} deficiency are listed in *Table 1*.[1-3,6,7]

Of particular interest to family physicians, an association between metformin

SORT: KEY RECOMMENDATIONS FOR PRACTICE

Clinical recommendation	*Evidence rating*	*References*
Because it is as effective as intramuscular vitamin B_{12} injections, high-dose oral vitamin B_{12} might be a reasonable choice for replacement in many patients with vitamin B_{12} deficiency, regardless of the etiology.	B	20
Vitamin B_{12} supplementation to reduce elevated serum homocysteine levels in patients with mild to moderate Alzheimer disease should not be given because it does not alter the rate of cognitive decline.	B	26
Vitamin B_{12} supplementation to reduce levels of serum homocysteine in high-risk patients is not recommended because it does not reduce cardiovascular mortality.	A	28-31

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, go to http://www.aafp.org/afpsort.xml.

(Glucophage) use and vitamin B_{12} deficiency has been observed. A multicenter trial of 390 patients with diabetes mellitus receiving insulin therapy who were randomized to receive metformin, 850 mg three times daily, or placebo assessed the risk of vitamin B_{12} deficiency and low vitamin B_{12} levels over four years.[7] Compared with placebo, patients taking metformin had an increased risk of vitamin B_{12} deficiency (number needed to harm = 14 per 4.3 years) and low vitamin B_{12} levels (number needed to harm = 9 per 4.3 years). The effect increased with the duration of therapy. Although it is not known if prophylactic vitamin B_{12} supplementation prevents deficiency, it seems prudent to monitor vitamin B_{12} levels periodically in patients taking metformin.

Table 1. Risk Factors for Vitamin B_{12} Deficiency

Decreased ileal absorption
Crohn disease
Ileal resection
Tapeworm infestation
Decreased intrinsic factor
Atrophic gastritis
Pernicious anemia
Postgastrectomy syndrome (includes Roux-en-Y gastric bypass)
Genetic
Transcobalamin II deficiency
Inadequate intake
Alcohol abuse
Older persons
Vegetarians (includes exclusively breastfed children of vegetarian mothers)
Prolonged medication use
Histamine H_2 blockers
Metformin (Glucophage)
Proton pump inhibitors

Information from references 1 through 3, 6, and 7.

Manifestations

Clinical manifestations of vitamin B_{12} deficiency are listed in *Table 2*.[1,2]

Although the classic hematologic expression of vitamin B_{12} deficiency is a megaloblastic macrocytic anemia characterized by an elevated mean corpuscular volume and mean corpuscular hemoglobin, and a peripheral smear containing macroovalocytes and hypersegmented neutrophils, up to 28 percent of affected patients may have a normal hemoglobin level, and up to 17 percent may have a normal mean corpuscular volume.[8] Although folate deficiency may also produce a megaloblastic anemia, it is less common in the United States because of required folate fortification of enriched grain and cereal products.[9] Clinical manifestations of megaloblastic anemia include pallor,

tachycardia, weakness, fatigue, and palpitations. The evaluation and management of macrocytosis has been recently reviewed in *American Family Physician* (http://www.aafp.org/afp/2009/0201/p203.html).

Unlike hematologic manifestations, the specific mechanism by which vitamin B_{12} deficiency affects the neurologic system is unknown. Common neurologic manifestations include paresthesias, weakness, gait abnormalities, and cognitive or behavioral changes.

Vitamin B_{12} crosses the placenta and is present in breast milk. Pregnant women with low or marginal levels of vitamin B_{12} are at increased risk of having children with neural tube defects.[10] Exclusively breastfed children of mothers with vitamin B_{12} deficiency are at increased risk of failure to thrive, hypotonia, ataxia, developmental delays, anemia, and general weakness.[11] Women at high risk of or with known vitamin B_{12} deficiency should supplement with vitamin B_{12} while pregnant or breastfeeding.[12,13]

Table 2. Clinical Manifestations of Vitamin B_{12} Deficiency

Cutaneous
Hyperpigmentation
Vitiligo
Gastrointestinal
Glossitis
Jaundice
Hematologic
Anemia (macrocytic, megaloblastic)
Thrombocytopenia
Neuropsychiatric
Cognitive impairment
Gait abnormalities
Irritability
Peripheral neuropathy
Weakness

Information from references 1 and 2.

Screening and Laboratory Assessment

Currently, the U.S. Preventive Services Task Force does not have published guidelines on screening asymptomatic adults for vitamin B_{12} deficiency.[14] Other major medical organizations do not have any recommendations for screening low-risk patients. Family physicians should consider screening patients who have any risk factors listed in *Table 1*.[1-3,6,7]

The initial laboratory assessment of a patient with suspected vitamin B_{12} deficiency should include a complete blood count and a serum vitamin B_{12} level. Several coexisting conditions may falsely lower serum B_{12} levels, including oral contraceptive use, multiple myeloma, pregnancy, and folate deficiency.[15] In contrast, falsely normal levels may be seen in patients with liver disease, myeloproliferative disorders, or renal disease.[15] Although many research studies and clinical laboratories define vitamin B_{12} deficiency at a level of less than 150 pg per mL (110.67 pmol per L), or in some cases 200 pg per mL, patients with values above these levels may be symptomatic and benefit from treatment.[1] Vitamin B_{12} levels greater than 350 pg per mL seem to be protective against symptoms of vitamin B_{12} deficiency.[15,16]

In patients with clinical symptoms of vitamin B_{12} deficiency and low levels of serum vitamin B_{12}, no further confirmatory testing is generally needed before treatment is initiated. Verification with serum methylmalonic acid and/or serum homocysteine level may be necessary in asymptomatic patients with high-risk conditions, symptomatic patients with low-normal levels of vitamin B_{12} (200 to 350 pg per mL), or symptomatic patients in whom vitamin B_{12} deficiency is unlikely but must be excluded. Elevated levels of serum homocysteine and methylmalonic acid have been shown to be highly sensitive markers for vitamin B_{12} deficiency. Testing is widely available,[5,8] but expensive, and multiple conditions may falsely elevate serum homocysteine and methylmalonic acid levels *(Table 3)*.[15] Because serum methylmalonic acid level is as sensitive as, but more specific than, serum homocysteine level for vitamin B_{12} deficiency, it is the confirmatory test of choice.[8,15] Serum holotranscobalamin level, which is reduced in vitamin B_{12}

Prolonged use of metformin appears to increase the risk of vitamin B_{12} deficiency.

Table 3. Causes of Falsely Elevated Serum Homocysteine and Methylmalonic Acid Levels

Homocysteine
Familial hyperhomocysteinemia
Folate deficiency
Levodopa therapy
Renal insufficiency
Methylmalonic acid
Renal insufficiency
Volume depletion

Information from reference 15.

deficiency, compared favorably with homocysteine and methylmalonic acid levels as a confirmatory test in one study, but further trials are needed before its widespread use for this purpose can be recommended.[17]

Pernicious anemia should be suspected in patients without an obvious cause of malabsorption or who have a coexisting autoimmune disorder, such as vitiligo or thyroiditis. The Schilling test, which was previously used to diagnose pernicious anemia, is no longer available in the United States, and testing for elevated levels of anti-intrinsic factor antibodies and elevated serum gastrin or pepsinogen is recommended.[18] Because of the association between pernicious anemia and a higher incidence of gastric cancer and carcinoids, it is important to pursue a diagnosis and, if confirmed, recommend endoscopy.[19]

Treatment

Treatment of clinical vitamin B_{12} deficiency has traditionally been accomplished by intramuscular injection of crystalline vitamin B_{12} at a dosage of 1 mg weekly for eight weeks, followed by 1 mg monthly for life.[1,2] In a 2005 Cochrane review, patients who received high dosages of oral vitamin B_{12} (1 to 2 mg daily) for 90 to 120 days had an improvement in serum vitamin B_{12} similar to patients who received intramuscular injections of vitamin B_{12}.[20] These results were consistent in patients regardless of the etiology of their vitamin B_{12} deficiency, including malabsorption states and pernicious anemia. Given the lower cost and ease of administration of oral vitamin B_{12}, this might be a reasonable choice for replacement in many patients. In cases of megaloblastic anemia, reticulocytosis generally occurs within a few days, and the hematocrit generally normalizes over several weeks.[21] Advanced neurologic symptoms may not respond to replacement.[1] Vitamin B_{12} has been demonstrated to be safe in doses up to 1,000 times the recommended dietary allowance and is safe in pregnancy.[21] The bioavailability of sublingual vitamin B_{12} appears to be equivalent to oral vitamin B_{12}, but there is no evidence that sublingual delivery offers any advantage over oral preparations.[22]

There are no clinical guidelines for the treatment of subclinical vitamin B_{12} deficiency (asymptomatic patients with decreased levels of vitamin B_{12} and elevated levels of homocysteine and/or methylmalonic acid). Physicians may opt to treat these patients and monitor for improvement of metabolic markers, particularly in populations at high risk of clinical vitamin B_{12} deficiency, or observe these patients and periodically reassess their levels of vitamin B_{12}, homocysteine, and/or methylmalonic acid. Patients with subclinical vitamin B_{12} deficiency will need at least 1 mg of vitamin B_{12} daily.[20,23]

Prevention

The Institute of Medicine estimates that adults younger than 50 years absorb approximately 50 percent of dietary vitamin B_{12}, and that between 10 and 30 percent of older patients may not be able to absorb adequate amounts from normal dietary sources.[21] The Institute of Medicine recommends daily consumption of 2.4 mcg of vitamin B_{12} in adults older than 18 years to prevent vitamin B_{12} deficiency. Because crystalline formulations are better absorbed than naturally occurring vitamin B_{12}, patients older than 50 years should consume foods fortified with vitamin B_{12} and vitamin B_{12} supplements, rather than attempting to get vitamin B_{12} strictly from dietary sources. Strict vegetarians must obtain their vitamin B_{12} from supplements or consumption of fortified cereal products to prevent deficiency.[21] Because of

the high incidence of vitamin B_{12} deficiency in patients undergoing gastric bypass surgery, daily prophylactic supplementation with 1 mg is recommended.[18,24]

Special Considerations

The American Academy of Neurology Practice Parameter on dementia lists vitamin B_{12} deficiency as a common comorbidity in older persons and recommends routine assessment of vitamin B_{12} levels in older patients with dementia.[25] No trials have specifically addressed the effects of treatment of vitamin B_{12} deficiency on dementia prevention or treatment. Trials have evaluated elevated homocysteine levels as a focus for potential treatment with vitamin B_{12} but did not note if the participants were also vitamin B_{12} deficient. Although treatment lowered serum homocysteine levels compared with placebo, no effect was seen on the progression of cognitive decline in patients with mild to moderate Alzheimer disease[26] or in preserving cognitive function in healthy adults.[27] Thus, it remains uncertain how vitamin B_{12} deficiency may be linked to dementia and what the potential benefits are of treatment with supplementation.

There has been a great deal of interest in the link between elevated levels of homocysteine, a direct consequence of vitamin B_{12} deficiency, and cardiovascular disease. No studies have directly evaluated the cardiovascular effects of correcting vitamin B_{12} deficiency in patients with known cardiovascular disease, although numerous studies have failed to demonstrate that correction of hyperhomocysteinemia itself reduces cardiovascular mortality or cardiovascular complications.[28-31] The routine use of vitamin B_{12} to lower levels of serum homocysteine in patients at high risk of cardiovascular events is not recommended.

Data Sources: A PubMed search was completed using the key terms vitamin B_{12} deficiency and cobalamin deficiency. Also searched were the Cochrane database and the National Guideline Clearinghouse database. Search date: July 2010.

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