

Update on Vitamin B12 Deficiency

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Abstract: Vitamin B12 (cobalamin) deficiency is a common cause of megaloblastic anemia, a variety of neuropsychiatric symptoms and elevated serum homocysteine levels, particularly in the elderly. There are a number of risk factors for vitamin B12 deficiency, including long-term use of metformin and proton pump inhibitors. No major medical organization, including the U. Preventive Services Task Force, has published guidance on screening for vitamin B12 deficiency in asymptomatic or low-risk adults, but high-risk patients, such as B. those with malabsorption disorders, can order a detection.

The initial laboratory evaluation of a patient suspected of having vitamin B12 deficiency should include a complete blood count and serum vitamin B12 level. can be used to confirm deficiency in asymptomatic, high-risk patients with low normal vitamin B12 levels. Because crystalline formulations are better absorbed than natural vitamin B12, patients over the age of 50 and strict vegetarians should consume vitamin B12-fortified foods and vitamin B12 supplements rather than attempting to obtain vitamin B12 from dietary sources only

Administering vitamin B12 to patients with elevated serum homocysteine levels has not been shown to decrease cardiovascular outcomes in high-risk patients or alter cognitive decline in patients with mild to moderate Alzheimer's disease.

Keywords: vitamin B12 deficiency, medical organization, decrease cardiovascular, moderate Alzheimer's disease.

I. INTRODUCTION

Vitamin B12 (cobalamin) is a water-soluble vitamin that is critical for normal neurological function, red blood cell production, and DNA synthesis. Vitamin B12 is essential for three enzymatic processes: the conversion of homocysteine into methionine; the conversion of methyl malonic acid to succinic coenzyme A; and the conversion of 5-

methyltetrahydrofolate to tetrahydrofolate, a process required for DNA synthesis and red blood cell production.¹ It cannot be made by humans and must be obtained regularly by ingesting animal protein or fortified grain products. Stomach acid releases vitamin B12 from animal proteins, after which it combines with intrinsic factor produced by the gastric parietal cells and is absorbed in the terminal ileum. Pernicious anemia, characterized by autoimmune-mediated chronic atrophic gastritis, is a classically described cause of vitamin B12 deficiency; Other common causes include postoperative malabsorption, nutritional deficiencies, and dietary vitamin B12 malabsorption.³ Due to large hepatic vitamin B12 stores, there can be a delay of 5 to 10 years between the onset of deficiency and the onset of vitamin B12 -Without deficiency, symptoms come clinically. In asymptomatic patients with low normal vitamin B12 levels (200 to 350 pg/mL [147.56 to 258.23 pmol per L]), elevated levels of the precursor compounds homocysteine and methyl malonic acid may lead to decisions to supplement patients with vitamin B12.⁵ The true prevalence of vitamin B12 deficiency is difficult to estimate based on reports based on Values that vary due to inclusion criteria and individual laboratory methodology. In 1994, the Framingham Heart Study reported the prevalence of vitamin B12 deficiency, defined as a serum vitamin B12 level of less than 200, pg. Per mL and elevated serum homocysteine, methyl malonic acid, or both, up to 12% in 548 elderly patients living in communities.⁶

However, most patients with deficiency had no hematological manifestations and no neurological manifestations were evaluated. According to unpublished data from the National Health and Nutrition Examination Survey, 3.2% of American adults age 50 and older are with an estimated serum vitamin B12 level of less than 200 pg per ml.¹ Risk factors for vitamin B12 deficiency are listed in Table 1.1-3,6,7 Of Particular Interest to Clinicians Runs in families, an association between metformin (Glucophage) and vitamin B12 deficiency has been observed. In a multicenter study of 390 patients with diabetes mellitus on insulin therapy who were randomized to receive either metformin 850 mg three times a day or placebo, the risk of vitamin B12 deficiency was assessed, with having low levels Vitamin B12 levels for four years.⁷ Compared to placebo, patients taking metformin had an increased risk of vitamin B12 deficiency (Numbers needed to cause harm = 14 per 4, 3 years) and low vitamin B12 levels 9 times 4.3 years). The effect increased with the duration of therapy. Although it is not known whether prophylactic vitamin B12 supplementation prevents deficiency, it is advisable to regularly monitor vitamin B12 levels in patients taking metformin.

SORT: KEY RECOMMENDATIONS FOR PRACTICE		
<i>Clinical recommendation</i>	<i>Evidence rating</i>	<i>References</i>
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.	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.	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.	28-31	
<i>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.</i>		

Table 1. Risk Factors for Vitamin B₁₂ Deficiency

Decreased ileal absorption
Crohn disease
Ileal resection
Tapeworm infestation
Decreased intrinsic factor
Atrophic gastritis
Pernicious anemia
Post gastrectomy 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
<i>Information from references 1 through 3, 6, and 7.</i>

Manifestations

Clinical manifestations of vitamin B₁₂ deficiency are listed in *Table 2*.^{1,2}

Although the classic hematological expression of vitamin B₁₂ deficiency is megaloblastic macrocytic anemia, characterized by increased mean corpuscular volume and mean corpuscular hemoglobin, and a peripheral smear containing macroovalocytes and hypersegmented neutrophils, up to 28 % of affected patients have normal blood glucose hemoglobin levels, and up to 17 percent may have normal mean corpuscular volume.⁸ Although folate deficiency can also cause megaloblastic anemia, it is more common in the United States because of the need for folate fortification from fortified grains and grain products less common.⁹ Clinical manifestations of megaloblastic anemia include pallor, tachycardia, weakness, fatigue and palpitations. The assessment and treatment of macrocytosis was recently reviewed in contrast to the hematological manifestations, the specific mechanism by which vitamin B₁₂ deficiency affects the neurological system is unknown. Common neurological manifestations include paraesthesia, weakness, gait disturbances, and cognitive or behavioral changes. Vitamin B₁₂ crosses the placenta and is found in breast milk. Pregnant women with low or marginal vitamin B₁₂ levels are at increased risk of having children with neural tube defects.¹⁰ Infants exclusively breastfed by vitamin B₁₂-deficient mothers are at increased risk of vitamin B₁₂ growth retardation, hypotonia, ataxia, developmental delays, anemia and general weakness.

¹¹ Women at high risk or known to be vitamin B₁₂ deficient should supplement vitamin B₁₂ during pregnancy or breastfeeding.^{12,13}

II. SCREENING AND LABORATORY ASSESSMENT

Currently, the U.S. Preventive Services Task Force does not have published guidelines on screening asymptomatic adults for vitamin B₁₂ 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 B₁₂

The deficiency must include a complete blood count and vitamin B₁₂ serum level. Several coexisting conditions can falsely lower serum B₁₂ levels, including oral contraceptive use, multiple myeloma, pregnancy, and folate deficiency.¹⁵

Conversely, falsely normal levels can be observed in patients with liver disease, myeloproliferative disorders, or kidney disease.¹⁵ Although many studies have been conducted Studies and clinical laboratories have defined a vitamin B12 deficiency of less than 150 pg per ml (110.67 pmol per L) or in some cases 200 pg per mL, patients with levels above these levels may present with symptoms and benefit from treatment.¹ Vitamin B12 levels greater than 350 pg per mL appear to precede vitamin B12 symptoms protect deficiency.^{15,16} In patients with clinical symptoms of vitamin B12 deficiency and low serum vitamin B12 levels, no further confirmatory testing is generally required prior to initiating treatment.

In asymptomatic patients with high-risk conditions, symptomatic patients with low normal levels of vitamin B12 (200 to 350 pg per mL), or symptomatic patients who may require testing with serum methylmalonic acid and/or serum homocysteine levels vitamin B12 -Deficiency is unlikely, but must be ruled out. Elevated levels of serum homocysteine and methylmalonic acid have been shown to be highly sensitive markers of vitamin B12 deficiency. Tests are widely available,^{5,8} but they are expensive, and several conditions can falsely raise serum levels. Homocysteine and methylmalonic acid levels (Table 3).

Because serum methylmalonic acid level is so sensitive but more specific than serum homocysteine level for vitamin B12 deficiency, it is the confirmatory test of choice.^{8,15} Holotranscobalamin level serum deficiency compared to -Cysteine favorably and methylmalonic acid levels as a confirmatory test in one study, but more studies are needed before its widespread use for this purpose can be recommended. ¹⁷ Pernicious anemia should be suspected in patients with no apparent cause of malabsorption or in patients with co-existing autoimmune disease. such as vitiligo or thyroiditis.

The Schilling test, previously used to diagnose pernicious anemia, is no longer available in the United States, and testing for elevated intrinsic factor antibodies and elevated serum gastrin or pepsinogen levels is recommended. ¹⁸ Because of the association between pernicious anemia and an increased incidence of gastric cancer and carcinoids, it is important to make a diagnosis and, if confirmed, to recommend endoscopy.¹⁹

Table 2. Clinical Manifestations of Vitamin B₁₂ Deficiency

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

<i>Information from references 1 and 2.</i>

III. TREATMENT

Treatment of clinical vitamin B₁₂ deficiency has traditionally been accomplished by intra- muscular injection of crystalline vitamin B₁₂ 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 B₁₂ (1 to 2 mg daily) for 90 to 120 days had an improvement in serum vitamin B₁₂ similar to patients who received intramuscular injections of vitamin B₁₂.²⁰ These results were consistent in patients regardless of the etiology of their vitamin B₁₂ deficiency, including malabsorption states and pernicious anemia. Given the lower cost and ease of administration of oral vita- min B₁₂, 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 B₁₂

has been demonstrated to be safe in doses up to 1,000 times the recommended dietary allowance and is safe in pregnancy.²¹ The bio avail ability of sublingual vitamin B₁₂ appears to be equivalent to oral vitamin B₁₂, 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 B₁₂ deficiency (asymptomatic patients with decreased levels of vitamin B₁₂ 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 B₁₂ deficiency, or observe these patients and periodically reassess their levels of vitamin B₁₂, homocysteine, and/or methylmalonic acid. Patients with subclinical vitamin B₁₂ deficiency will need at least 1 mg of vitamin B₁₂ daily.^{20,23}

IV. PREVENTION

The Institute of Medicine estimates that adults younger than 50 years absorb approximately 50 percent of dietary vitamin B₁₂, 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 B₁₂ in adults older than 18 years to prevent vitamin B₁₂ deficiency. Because crystalline formulations are better absorbed than naturally occurring vitamin B₁₂, patients older than 50 years should consume foods fortified with vitamin B₁₂ and vitamin B₁₂ supplements, rather than attempting to get vitamin B₁₂ strictly from dietary sources. Strict vegetarians must obtain their vitamin B₁₂ from supplements or consumption of the high incidence of vitamin B₁₂ deficiency in patients undergoing gastric bypass surgery, daily prophylactic supplementation with 1 mg is recommended.^{18,24}

V. SPECIAL CONSIDERATIONS

The American Academy of Neurology Practice Parameter on dementia lists vitamin B₁₂ deficiency as a common comorbidity in older persons and recommends routine assessment of vitamin B₁₂ levels in older patients with dementia.²⁵ No trials have specifically addressed the effects of treatment of vitamin B₁₂ deficiency on dementia prevention or treatment. Trials have evaluated elevated homocysteine levels as a focus for potential treatment with vitamin B₁₂ but did not note if the participants were also vitamin B₁₂ 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 disease²⁶ or in preserving cognitive function in healthy adults.²⁷ Thus, it remains uncertain how vitamin B₁₂ 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 B₁₂ deficiency, and cardiovascular disease. No studies have directly evaluated the cardiovascular effects of correcting vitamin B₁₂ deficiency in patients with known cardiovascular disease, although numerous studies have failed to demonstrate that correction of hyper homocysteinemia itself reduces cardiovascular mortality or cardiovascular complications.²⁸⁻³¹ The routine use of vitamin B₁₂ 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 B₁₂ deficiency and cobalamin deficiency. Also searched were the Cochrane database and the National Guideline Clearinghouse database. Search date: Feb 2022.

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