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Vitamin B₁₂: No One Should Be Without It



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Vitamin B₁₂ status is dependent on a variety of factors including dietary or supplemental intake, intestinal absorption, hepatic function and drug-induced depletion. While vitamin B₁₂ deficiency is often recognized in certain conditions (such as macrocytic anemia and ileal resection), the incidence and symptoms may go unnoticed in other high-risk populations, especially the elderly. Diagnosis may be difficult as symptoms can be non-specific and available diagnostic tests have limitations. This article will discuss the nutritional needs and sources of vitamin B₁₂, factors that affect absorption, and how to best monitor and replace vitamin B₁₂ in those who are deficient. The relationship between vitamin B₁₂ and folate will also be reviewed.

INTRODUCTION

Vitamin B₁₂ (also known as cobalamin, or simply B₁₂) is a water soluble vitamin necessary for normal neurological function and formation of red blood cells. B₁₂ is also a cofactor in two metabolic pathways, specifically the conversion of homocysteine to methionine and the conversion of methylmalonic acid (MMA) to succinyl-CoA.

Sources of B₁₂ include animal products (such as meat, fish, poultry, shellfish, and milk), fortified foods (most commonly ready to eat breakfast cereals),

and B₁₂ supplements. The Recommended Daily Allowance (RDA) for B₁₂ is shown in Table 1. No Tolerable Upper Intake Limit (UL) has been set for B₁₂ as there is little evidence of toxicity and insufficient data to support an UL (1).

Based on the average American diet, B₁₂ intake often meets or exceeds the RDA; however, absorption of B₁₂ must also be considered. Strict vegetarians, those taking certain medications, patients with certain gastrointestinal conditions, anyone with poor overall intake, and anyone over age 50 may be at risk for inadequate intake or compromised absorption of B₁₂.

B₁₂ DEFICIENCY

Depending on the criteria used, the incidence of B₁₂ deficiency ranges from 5%–60%, but is likely around

(continued on page 39)

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(continued from page 34)

Table 1
RDA for Vitamin B₁₂ in Adults (1)*

Age (years)	Males/Females (µg/day)	Pregnancy (µg/day)	Lactation (µg/day)
19 and older	2.4	2.6	2.4
50 and older	2.4 (the majority from fortified food or a supplement)	N/A	N/A

*Of note, the % Daily Value (DV) used on current food labels is based on 6 µg/day. For example, if the food label states that a fortified food provides 50% of the DV for vitamin B₁₂, the food provides 3 µg/day.

20% in the general population (2,3). The signs of B₁₂ deficiency can be difficult to recognize because symptoms are often non-specific and absent altogether in older adults. The most common symptoms of B₁₂ deficiency are shown in Table 2. It is important to recognize the clinical significance of a deficiency because (unlike most other deficiencies), it can result in permanent damage. A deficiency can cause neuronal demyelination and axonal degeneration, and if left untreated, will eventually result in neuronal death. Therefore, early diagnosis and timely treatment are imperative (4).

SCREENING AND DIAGNOSIS

Currently, there is no agreed upon standard for screening for B₁₂ deficiency. Recommendations vary from screen all at risk individuals to treat all individuals. Certainly patients with gastrointestinal disorders, chronic poor nutritional intake, or signs of deficiency should be screened for B₁₂ deficiency. One recommendation is to screen all individuals at age 50, then every five years until age 65, and then annually (4).

The diagnosis of B₁₂ deficiency is often made based on serum markers. Currently, the most promising marker for B₁₂ status is serum holotranscobalamin (Holo TC) (5); unfortunately this test is not yet readily available. Currently, serum B₁₂ levels are the most frequently used biomarker of B₁₂ status. Controversy exists, however, regarding what the optimal level should be. Laboratory reference ranges vary greatly, but it is generally accepted that levels below 221 pmol/L (300 pg/mL) suggest a tissue level deficiency based on biochemical evidence of elevated homocysteine

and methylmalonic acid levels (see section below) (6). Serum B₁₂ levels can be significantly increased due to liver disease, certain cancers, chronic bone disease, or acute illness (7). Mean corpuscular volume is sometimes used for screening and diagnosis, but misses more than 80% of cases of B₁₂ deficiency (8).

Metabolites of pathways dependent on B₁₂ are sometimes used as surrogate markers to evaluate B₁₂ status. B₁₂ is necessary for the conversion of homocysteine to methionine, therefore increased homocysteine levels with concomitant low B₁₂ levels could indicate inadequate B₁₂ status; however, because folate, vitamin B₆ and betaine are also required for this pathway, elevated homocysteine levels are not specific to B₁₂ deficiency and therefore cannot be used for primary diagnosis. B₁₂ alone is required for the conversion of methylmalonic acid (MMA) to succinyl-CoA; therefore, a MMA level has been viewed as the gold standard in the evaluation of B₁₂ status. However, since the MMA assay is expensive, not readily available, and is altered by renal insufficiency, its utility has been questioned.

Table 2
Common Symptoms of B₁₂ Deficiency

- Neuropathic
 - Paresthesias, numbness, weakness
- Myelopathic
 - Abnormal gait, ataxia
- Cerebral
 - Dementia, depression, memory loss
- Hematologic – Anemia (uncommon)

Given the lack of specific, sensitive and readily available diagnostic tests, combined with the low risk of providing B₁₂ supplementation, it may be prudent in some cases (e.g. those chronically taking metformin, gastric acid suppressive agents or living with cirrhosis) to empirically provide supplemental B₁₂.

ABSORPTION AND SOURCES

The majority of B₁₂ is absorbed through a complex process requiring normal functioning of several areas of the GI tract. In the normal healthy stomach, pepsin and hydrochloric acid separate B₁₂ from protein, thereby releasing it for absorption. The free B₁₂ then combines with R-proteins released from the salivary glands and gastric mucosa. The B₁₂-R-protein complex moves into the small bowel where the alkaline environment and pancreatic enzymes again release the B₁₂ from the protein complex. The released B₁₂ then binds with gastrically produced intrinsic factor (IF) in the proximal small bowel and travels to the ileum where the B₁₂-IF complex binds to receptors for final absorption.

Two Avenues for Absorption

Naturally occurring B₁₂ is only found bound to protein of animal origin. In this form, B₁₂ must be cleaved from protein in order to be available for absorption; this requires normal levels of gastric secretions, including hydrochloric acid and pepsin. B₁₂ that is unbound (i.e. synthetic) can be absorbed via the IF route and can also be absorbed through passive diffusion throughout the GI tract. This passive diffusion route allows for the absorption of 1%-2% of unbound B₁₂. Both types of absorption occur simultaneously. Under normal conditions, the 1%-2% of B₁₂ absorbed by the passive diffusion route may be insignificant. However, this route becomes very important for those who lack intrinsic factor or have inadequate ileal receptors. Synthetic B₁₂ is found in fortified foods (such as fortified breakfast cereals, breads, and other products) and in oral supplements.

Alterations in B₁₂ Absorption

Due to the complex process required to absorb naturally occurring B₁₂, any disorder or alteration in normal gas-

tric or intestinal function can lead to malabsorption. In fact, approximately 20%-50% of those over the age of 50 are unable to absorb protein-bound B₁₂ (1). Conditions that can lead to alteration in B₁₂ absorption are listed in Table 3. The most common causes for altered B₁₂ absorption are underlying gastrointestinal disorders.

GASTRIC DISORDERS

Because B₁₂ absorption is dependent on several factors produced in the stomach, any alteration to normal gastric anatomy or function can affect absorption. The most common cause of malabsorption of naturally occurring (protein-bound) B₁₂ is hypochlorhydria (2). This type of malabsorption is characterized by a B₁₂ deficiency in the presence of sufficient dietary B₁₂ intake and a normal Schilling test. An acidic environment is required for the cleavage of B₁₂ from protein-bound food sources; in the absence of sufficient acid, B₁₂ remains protein-bound and passes throughout the GI tract unabsorbed.

Hypochlorhydria is caused primarily by atrophic gastritis and is especially common in adults over age 50. The incidence of hypochlorhydria in this population is estimated to be 20%-50% (10). Due to the high incidence of older adults unable to absorb protein

Table 3
Conditions That Can Affect B₁₂ Absorption

- Pernicious Anemia
- Hypochlorhydria due to atrophic gastritis
- Partial or total gastrectomy
- Bariatric Surgery
- Ileal Resection of >20 cm (9)
- Malabsorptive Disorders
- Short Bowel Syndrome
- Inflammation of the Ileum
 - Crohn's Disease
 - Celiac Disease
- Chronic Alcoholism
- Chronic pancreatitis
- Bacterial Overgrowth
- Whipple's disease
- Medications
 - Metformin
 - Gastric acid suppressive agents

bound B₁₂, the Dietary Reference Intake for people over the age of 50 includes the recommendation that the majority of B₁₂ should come from fortified foods or supplements (which is not protein-bound and therefore more easily absorbed).

Total or partial gastrectomy or bariatric surgery, may result in damage or removal of the cells that produce hydrochloric acid and intrinsic factor. Diseases that lead to hypersecretion of gastric acid may alter normal small bowel pH and may also affect B₁₂ absorption. Patients with any type of gastric surgical history or gastric disorders should be monitored closely for B₁₂ deficiency or empirically supplemented with adequate levels of synthetic B₁₂ (11,12).

Pernicious Anemia

Pernicious anemia is a megaloblastic anemia caused specifically by impaired B₁₂ absorption due to atrophic gastritis and a lack of parietal cells (which produce intrinsic factor). Pernicious anemia is responsible for about 15%–20% of cases of B₁₂ deficiency (2). Pernicious anemia has a gradual onset and usually develops over many years. Neurologic symptoms consistent with B₁₂ deficiency may be present before macrocytic anemia becomes clinically apparent; the best diagnostic test for pernicious anemia remains a matter of debate. Parietal cell or anti-intrinsic factor antibodies are sometimes used, however, neither one of these alone has both a high specificity and sensitivity (2). A Schilling test, especially in combination with anti-intrinsic factor antibody levels, may confirm the diagnosis (2). However, the Schilling test, which measures absorption of B₁₂, is difficult to perform, expensive (approximately \$375), and no longer widely used (13). Full, in-depth reviews of pernicious anemia are available elsewhere (3,14).

INTESTINAL DISORDERS

Disorders or alterations of the small bowel may also affect B₁₂ absorption. Normally, the majority of B₁₂ is absorbed in the ileum through the B₁₂-IF active transport route. Therefore surgical removal or bypass of significant amounts of the ileum (>20 cm) for any reason, may leave a patient dependent on some sort of B₁₂ supplementation (9). Inflammatory processes of the small bowel (such as Crohn's disease) commonly

affect the ileal portion of the intestine and can also affect absorption. Other causes of inflammation and malabsorption of B₁₂ include radiation enteritis, AIDS, and lymphoma. Patients with short gut may be lacking adequate ileum and total surface area to absorb sufficient amounts of any form of B₁₂. Chronic alcoholism may lead to decreased B₁₂ absorption due to atrophy of the small bowel villi (15).

Chronic pancreatic insufficiency can also lead to malabsorption of B₁₂. Insufficient pancreatic secretion can impede the cleavage of B₁₂ from the B₁₂-R-protein complex; this separation is required for the formation of the B₁₂-IF complex (3).

Small bowel bacterial overgrowth may also impact B₁₂ status, as the bacteria bind B₁₂ for their own use. Patients at risk for small bowel bacterial overgrowth include, but are not limited to, those with hypochlorhydria, intestinal dysmotility, intestinal obstructions or adhesions, intestinal diverticuli, blind loops of bowel due to past surgery, and those without an intact ileocecal valve.

Of note, individuals receiving jejunal tube feedings (who otherwise have an intact gastrointestinal tract) are able to absorb adequate B₁₂, despite being fed beyond the stomach. In such cases, the synthetic B₁₂ present in the tube feeding combines with intrinsic factor within the lumen of the small bowel and is absorbed normally in the ileum (16).

LIVER DISEASE

Ninety percent of B₁₂ is stored in the liver. Stores can last between one and five years depending on the amount consumed, absorbed, and hepatic function. Patients with liver disease are at risk of B₁₂ deficiency developing sooner than individuals with normal liver function because of a diminished storage capacity.

Interestingly, serum B₁₂ levels can be significantly elevated in the setting of hepatic disease or injury; hepatocyte degradation causes the release of stored B₁₂. Paradoxically, serum levels rise despite tissue levels being depleted (confirmed by liver biopsy studies) (7). In situations of significantly elevated B₁₂ levels due to hepatic disease or cancer, the clinician should be aware that this marker may not reflect actual stores; in this situation measuring MMA levels can help confirm a tissue level deficiency (7).

MEDICATIONS

Metformin

Certain medications may also affect B₁₂ status. The chronic use of metformin for diabetes can lower B₁₂ levels sufficiently to be of clinical significance (17). This is of particular concern because the peripheral neuropathy associated with B₁₂ deficiency can easily be confused with a diabetic neuropathy. According to the literature, 10%–30% of patients receiving metformin show signs of decreased B₁₂ absorption (18). The exact mechanism for this association remains unclear, but the most likely theory is antagonism at the ileal receptor sites. Ting, et al identified 155 patients with a B₁₂ deficiency (diagnosed by low serum B₁₂ levels) while taking metformin (19). They compared this group with 310 controls with normal serum B₁₂ and found that higher doses and prolonged administration (3 years or more, $p = < 0.001$ and $p = 0.001$ respectively) of metformin therapy were associated with an increased risk of B₁₂ deficiency.

Gastric Acid Suppressive Agents

Of growing concern is the effect that prolonged use of proton pump inhibitors (PPIs) or H₂-receptor antagonists (H₂-RAs) may have on B₁₂ status. These medications are often used for prolonged periods to treat a variety of gastrointestinal conditions and their recent switch to over-the-counter status further increases usage. Numerous studies have shown that these medications cause malabsorption of protein-bound B₁₂, likely due to the creation of a hypochlorhydric state. However, there has been some controversy as to whether this decrease in absorption results in a clinically significant deficiency. Dharmarajan, et al reviewed the records of 659 older adults, aged 60–102, and found that 54% used acid suppressing medication (4). The average length of treatment was 18 months. They found that prolonged use of PPIs did affect serum B₁₂ levels ($p = 0.0125$), and that this decrease in serum B₁₂ levels occurred despite oral supplementation with RDA levels of B₁₂. Valuck, et al also reviewed the charts of patients over the age of 65 and compared those with documented B₁₂ deficiency ($n = 53$) with a control group with normal B₁₂ status ($n = 212$) (20). This retrospective study

found that chronic use of PPIs or H₂-RAs was significantly associated with B₁₂ deficiency. The absence of a consistent demonstration of B₁₂ deficiency in all studies may reflect the short duration of these studies and the long half-life of this nutrient. In the presence of adequate B₁₂ stores, it can take years for a deficiency to develop. Although more prospective, randomized, controlled studies are needed, these studies suggest that monitoring B₁₂ status among patients on chronic PPIs and H₂-RAs would be wise.

TREATMENT

Regardless of the cause of B₁₂ deficiency, oral replacement is feasible in most cases. Indeed, in Sweden, high dose oral therapy has been in use for three decades and represents 80% of B₁₂ replacement costs (21). Most people can absorb synthetic B₁₂ efficiently (compared with protein-bound B₁₂ in animal foods) (22). Oral therapy (compared to the parenteral route) is less expensive, more convenient, less uncomfortable, and well accepted by patients (23). The traditional oral dose to treat a deficiency is 1000–2000 µg/day (24). Recommendations for the duration of this replacement level vary from one-to-four weeks (2,13) (Table 4). Oral B₁₂ is available over the counter as sustained release tablets, sublingual tablets, granules, or oral strips (25,26) in 250 µg, 500 µg, or 1000 µg dosages. A B₁₂ supplement in the form of a nasal spray is also marketed (www.nascobal.com), but may not be readily available in some areas (based on a survey of local pharmacies and health food stores in our area). Patients prescribed oral B₁₂ replacement should be monitored to ensure compliance and adequate response to treatment.

Intramuscular (IM) B₁₂ has long been the standard treatment for pernicious anemia, however many clinicians are unaware that pernicious anemia can be treated with high dose oral B₁₂ therapy. When oral/enteral synthetic B₁₂ is provided in high doses, adequate amounts can be absorbed via the passive diffusion route and the lack of intrinsic factor becomes moot. Such therapy is as effective and may be superior to parenteral supplementation. In Kuzminski's clinical trial ($n = 28$) newly diagnosed B₁₂ deficient patients were randomized to receive either 1mg of parenteral

(continued on page 45)

(continued from page 42)

Table 4
Deficiency (2,13) and Maintenance Doses of B₁₂ (2,3)

Deficiency		
Oral (synthetic)	1000 µg/day for 1–4 weeks	
Parenteral	1000 µg/day for 1 week	
Maintenance		
	<i>Food-cobalamin malabsorption</i>	<i>Pernicious Anemia or No Ileal Receptors</i>
Oral (synthetic)	125–500 µg/d	1000 µg/d
IM	1000 µg/month	

or 2 mg oral B₁₂. Four months after the treatment period, the investigators found that those receiving daily high dose oral therapies had higher serum B₁₂ levels ($p < 0.0005$) and lower methylmalonic acid levels ($p < 0.05$) than the parenteral group (27).

However, there are some clinical conditions in which oral replacement may not be reliable because of a lack of clinical trials to demonstrate efficacy. For example, in ileal resection, active inflammation of the bowel, or severe short bowel disease, oral replacement may not be effective. Patients with a history of poor adherence with oral medication regimens may also require parenteral treatment. When oral replacement is not possible or practical, parenteral IM injections are the mainstay of therapy. See Table 4 for replacement guidelines.

Of note, the amount of B₁₂ absorbed or retained is directly related to the dose provided (1). In naturally-occurring levels and when low doses (<5 µg) of synthetic B₁₂ are provided, the absorption rate is 50%–60%. When dosages rise above 500 µg, absorption rates drop to 1%. The same is true for IM B₁₂; at doses below 40 µg, 93%–100% is retained and with a 1000 µg dose, only 15% is retained. Despite this drop in absorption and retention rate however, the amounts utilized remain well above the RDA of 2.4 µg/day. While this may mean that lower doses could be used to replete B₁₂ stores, more research is needed before such recommendations can be made. There are no large, long term studies looking at outcomes and patient response to lower doses. Because of this lack of data, along with concerns that oral B₁₂ supplements may vary in compo-

sition and the low likelihood of any adverse effects from higher doses, the recommendations currently remains to supplement with levels shown in Table 4.

PREVENTION AND MAINTENANCE

Once a deficiency has been corrected or a risk factor has been identified, individuals with conditions that put them at continued risk for B₁₂ deficiency should receive ongoing supplementation to maintain levels and prevent further deficiency. Table 4 shows recommendations for maintenance doses of B₁₂. The exact dose required to counteract drug-induced malabsorption has yet to be determined; however it is likely doses far greater than the RDA are required (6). Those with pernicious anemia or an absence of ileal receptors need high dose oral therapy (1000 µg/day) to ensure adequate B₁₂ absorption by passive diffusion. Patients at risk for deficiency will need continued maintenance replacement for life unless the underlying cause of the deficiency can be corrected.

In general, oral supplementation is preferred for maintenance of B₁₂ levels in those at risk for deficiency. However, some patients may prefer an IM injection every one-to-three months versus a daily oral supplement. The cost of various forms of B₁₂ supplementation is shown in Table 5.

FOLATE AND B₁₂

Both folate and B₁₂ are required for normal cell maturation, a deficiency of either leads to ineffective, dysplastic erythropoiesis. Folate and B₁₂ are also united in the methionine cycle. Inadequate folate blocks action of B₁₂ and vice versa.

Folic acid supplementation can mask a B₁₂ deficiency by reversing the anemia. However, neurological complications can be precipitated if there is marginal B₁₂ status and permanent neurological damage is possible. Therefore, some precautions should be taken before beginning a folic acid supplement. B₁₂ level should be checked, or there is little risk to simply adding a B₁₂ supplement. Examples of conditions where folic acid supplementation is sometimes recommended include: hyperhomocysteine therapy for cardiovascular disease, alcoholism, sickle cell anemia, and Crohn's and celiac disease.

Table 5
Cost Comparison of B₁₂ Supplements

B ₁₂ Formulation	# Doses/month	Average cost per month
IM injection (cost of syringes not included)*	1	\$8.35 (1000 µg dose) or 0.28 cents/day**
Capsule***	30	\$1.11 (1000 µg per day)

*University of Virginia Health System Outpatient Pharmacy

**Important to note that these costs do not reflect the added cost to the patient and health care system for the office visit required to administer the IM dose or the added burden of travel for those with impaired mobility, etc.

***Wal-Mart 2008

CONCLUSION

B₁₂ deficiency is not uncommon and often goes unrecognized. Early recognition and treatment is crucial as, unlike most other nutrients, untreated B₁₂ deficiency can result in significant morbidity and irreversible neurologic damage. The elderly, those with gastrointestinal disorders and individuals taking certain medications are at higher risk for developing a deficiency. In fact, because the elderly are at much greater risk, it is recommended by some that all adults over age 50 receive a synthetic source of B₁₂ daily.

In 2009, no one should become B₁₂ deficient. ■

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