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# Vitamin B12: Identification and Treatment of Deficiencies

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Vitamin B<sub>12</sub>: Identification and Treatment of Deficiencies

Max E. Mitchell

An evidence-based scholarly paper submitted to the faculty of  
Brigham Young University  
in partial fulfillment of the requirements for the degree of

Master of Science

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## ABSTRACT

### Vitamin B<sub>12</sub>: Identification and Treatment of Deficiencies

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Vitamin B<sub>12</sub> is essential for the proper functioning of all cells. A deficiency can cause serious hematologic and neurologic damage. Groups at high risk for developing vitamin B<sub>12</sub> deficiency include the elderly, vegetarians, pregnant women, persons with pernicious anemia, and patients with a history of gastrointestinal (GI) surgery. The purpose of this article is to increase awareness of vitamin B<sub>12</sub> deficiency and discuss its pathophysiology, symptoms, diagnostic testing, and management.

Keywords: Vitamin B<sub>12</sub>, cobalamin, deficiency, risk factors, symptoms, management

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## Vitamin B<sub>12</sub>: Identification and Treatment of Deficiencies

Vitamin B<sub>12</sub>, also known as cobalamin, is a water-soluble vitamin containing cobalt, a compound essential for maintaining the health of all cells because it is needed for production of DNA and RNA, the body's genetic material.<sup>1</sup> Vitamin B<sub>12</sub> is especially important in maintaining the health of the body's nerve and blood cells.<sup>2-4</sup> Specifically, it is crucial for maintaining healthy nerve cells<sup>4</sup> and supporting bone marrow production of red blood cells (RBCs).<sup>2</sup>

Deficiency of vitamin B<sub>12</sub> can lead to serious complications in hematologic and neurologic systems.<sup>5,6</sup> Causes of deficiency include inadequate intake, absorption, and transport.<sup>2</sup> Recognizing a deficiency and providing prompt treatment is essential to preventing severe hematologic issues and possibly irreversible neurologic damage due to demyelination.<sup>5-7</sup>

Vitamin B<sub>12</sub> deficiency is a disorder that affects a significant number of adults, particularly those in high-risk groups. In fact, it is estimated that 3% to 40% of the general population is deficient in vitamin B<sub>12</sub> (depending on the diagnostic criteria used), and an additional 15% over the age of 60 are believed to be undiagnosed.<sup>2,8,9</sup> Although vitamin B<sub>12</sub> deficiency can affect persons of all ages, the incidence of deficiency increases with age.<sup>5,6</sup> Other groups at high risk for vitamin B<sub>12</sub> deficiency include vegetarians, pregnant women, those with pernicious anemia, and patients with a history of gastrointestinal (GI) surgery.<sup>1,2,3,10</sup> Strict vegans are at particular risk for developing a vitamin B<sub>12</sub> deficiency and are 10 times more likely than vegetarians, and 50 times more likely than the general population, to develop a deficiency.<sup>1</sup>

As primary care providers, Nurse Practitioners (NPs) treat patients across the lifespan and should be aware of vitamin B<sub>12</sub> deficiency as a potential diagnosis in high-risk groups of all ages. The purpose of this article is to provide NPs with an overview of the importance of vitamin B<sub>12</sub>,

how to identify those at risk and recognize a deficiency, and to provide a guideline for treatment management and education for patients with this condition.

## **VITAMIN B<sub>12</sub> DEFICIENCY**

### **Pathophysiology**

To understand vitamin B<sub>12</sub> deficiency, it is helpful to first understand the basic process by which vitamin B<sub>12</sub> (cobalamin) is utilized in the body. Once ingested, cobalamin is released from the food complex by pepsin and hydrochloric acid in the stomach.<sup>5</sup> The free cobalamin binds to a glycoprotein in saliva (gastric R binder), and the complex moves into the duodenum and jejunum where pancreatic enzymes break down the complex and release cobalamin.<sup>11</sup> Cobalamin then binds to intrinsic factor, which is secreted from the parietal cells of the stomach.<sup>6,11</sup> Once bound with intrinsic factor, the compound becomes Cobalamin-Intrinsic Factor (CIF) complex, which is then absorbed in the distal ileum, releasing cobalamin into the plasma.<sup>6,11</sup> There must be sufficient dietary intake of vitamin B<sub>12</sub>, acid-pepsin in the stomach, pancreatic proteases, functional intrinsic factor, functioning CIF receptors in the ileum, and an intact upper GI tract for adequate absorption to occur.<sup>6</sup> A disorder in any of these areas can result in vitamin B<sub>12</sub> deficiency.<sup>5,6,11</sup>

### **Risk Factors**

Although vitamin B<sub>12</sub> deficiency can occur among the general population, it is important for NPs to be aware of high-risk groups to avoid a delay in diagnosis and treatment. Although traditionally considered a disorder of the elderly, research has shown that vegetarians and vegans, pregnant women, those with pernicious anemia, and individuals with a history of GI surgery are also at an increased risk for a deficiency.<sup>3,12</sup> It is important, therefore, not only to recognize these individuals but to understand how different risk factors contribute to a vitamin

B<sub>12</sub> deficiency. This understanding is essential when developing a management plan appropriate for the individual.

**Older Adults.** Vitamin B<sub>12</sub> deficiency occurs frequently in older adults, especially those in their 70s and 80s, and is usually due to malabsorption of food-bound vitamin B<sub>12</sub>.<sup>2,8,13</sup> As individuals age, atrophic gastritis and bacterial overgrowth of the GI tract can either individually or in combination cause reduced gastric acid production, resulting in malabsorption of food-bound vitamin B<sub>12</sub>.<sup>8</sup> Hvas suggests age-related gastric atrophy also contributes to malabsorption.<sup>12</sup> Chronic atrophic gastritis, which affects as many as 30% of older adults, is a condition that results in the degeneration and thinning of the stomach wall, leading to gastric cell atrophy and a decrease in the production of stomach acids, thus minimizing the body's ability to absorb vitamin B<sub>12</sub>.<sup>2,3,13</sup> Therefore, elderly individuals with a vitamin B<sub>12</sub> deficiency might not be able to adequately absorb oral vitamin B<sub>12</sub> replacements. This should be considered when discussing treatment options.

**Vegetarians.** Vegetarians and vegans are at high risk for developing a vitamin B<sub>12</sub> deficiency because they do not ingest foods of animal origin, such as meat and dairy products, which contain vitamin B<sub>12</sub>. It was once thought that only strict vegans lacked adequate intake of vitamin B<sub>12</sub> containing foods, however, it is now known that deficiencies can be found among persons observing all types of vegetarian diets, including lacto-ovo-vegetarians.<sup>14</sup> Although vegetarians and vegans might vary in their consumption of the types of foods that contain vitamin B<sub>12</sub>, a vegetarian or vegan diet that does not allow for adequate amounts of vitamin B<sub>12</sub> will influence their management plan.

**Pregnancy.** Vitamin B<sub>12</sub> is essential for cell multiplication during pregnancy because of its important role in DNA synthesis.<sup>10</sup> Although pregnancy itself does not cause a deficiency,

pregnant women with low vitamin B<sub>12</sub> levels might be at higher risk for giving birth to a baby with adverse fetal and neonatal outcomes, primarily neural tube defects.<sup>10</sup> Pregnant women have the same risk for vitamin B<sub>12</sub> deficiency as the general population, or might be at greater risk due to dietary restrictions. However, identifying women at risk or with a deficiency prior to pregnancy is crucial to ensure that essential DNA synthesis can occur and to prevent or minimize adverse fetal outcomes.<sup>10</sup>

***Pernicious Anemia.*** Patients with pernicious anemia are at high risk for developing a vitamin B<sub>12</sub> deficiency.<sup>7</sup> Pernicious anemia is an autoimmune condition resulting from the destruction of gastric parietal cells and the associated lack of intrinsic factor needed to bind ingested vitamin B<sub>12</sub>.<sup>7</sup> Without intrinsic factor, vitamin B<sub>12</sub> absorption is limited to a very small amount through passive diffusion. The absence of intrinsic factor might be congenital or a developed condition, as seen in atrophic gastritis.<sup>2</sup> Those at risk for pernicious anemia are adults aged 50 to 60 years, women, and those of African or European descent.<sup>2,7</sup> The inability of individuals with pernicious anemia to absorb vitamin B<sub>12</sub> from food will also influence their management plan.

***Gastrointestinal Surgery.*** Individuals who have undergone some types of gastrointestinal surgery are at greater risk for a vitamin B<sub>12</sub> deficiency as a result of the surgery.<sup>2</sup> A total gastrectomy leads to a loss of cells that secrete pepsin or intrinsic factor and hydrochloric acid, resulting in an inability to absorb vitamin B<sub>12</sub>. Partial gastrectomy also causes decreased vitamin absorption because it leads to the development of atrophic gastritis.<sup>2,3</sup> Just as in the elderly who develop atrophic gastritis, partial gastrectomy patients develop gastric cell atrophy and a decrease in the production of stomach acids, minimizing the body's ability to absorb vitamin

B<sub>12</sub>.<sup>2,3,13</sup> When developing a treatment plan for patients with a history of GI surgery, their inability to absorb vitamin B<sub>12</sub> from food should be considered.

### **Presentation**

Patients with a vitamin B<sub>12</sub> deficiency might be asymptomatic or present with symptoms that range from mild to severe. Symptoms usually develop over several years and are often vague.<sup>2,4,6</sup> It is important that NPs include vitamin B<sub>12</sub> deficiency as part of their differential diagnosis when patients present with any of the following symptoms (Table 1).

Table 1.

#### Common Symptoms of Vitamin B<sub>12</sub> Deficiency

|  |
|--|
| <i>Eyes:</i> Loss of central vision; pale conjunctiva  |
| <i>Oral:</i> Enlarged inflamed tongue; mucosal ulceration(s)   |
| <i>Skin:</i> Jaundice; pigment changes   |
| <i>GI:</i> Loss of appetite; digestive issues  |
| <i>Hematologic:</i> Anemia   |
| <i>Neurological:</i> Impaired gait and balance; peripheral paresthesia and numbness to hands and feet; generalized weakness; loss of position and vibratory sense; dizziness |
| <i>Cognitive:</i> Impaired memory and concentration  |
| <i>Behavioral:</i> Anxiety; depression   |

Adapted from Candela and Meiner<sup>2</sup> Snyder<sup>15</sup> and Orton<sup>6</sup>

### **Physical Examination**

There are no classic clinical manifestations or "gold standard" available to assist in making a diagnosis of vitamin B<sub>12</sub> deficiency. In fact, symptoms might be attributed to other

diagnoses.<sup>15</sup> A thorough history can help the NP identify risk factors and develop appropriate differential diagnoses, thus focusing the physical examination.<sup>2</sup> For instance, when examining an elderly patient, the NP should watch for even the smallest signs of neurologic or cognitive dysfunction, which might otherwise be attributed to early signs of dementia.<sup>16</sup> In other words, when a patient in a risk group for a vitamin B<sub>12</sub> deficiency presents with symptoms consistent with a deficiency, the NP should focus the physical examination on other signs of deficiency including jaundice, oral manifestations, or neurological changes as outlined in Table 1. Early suspicion of vitamin B<sub>12</sub> deficiency can lead to early diagnosis and treatment, eliminating the development of potentially serious neurological and hematological complications.<sup>6</sup>

### **Diagnostic Testing**

Patients who belong to high-risk groups, or those with signs and symptoms consistent with a vitamin B<sub>12</sub> deficiency, should be evaluated. A serum cobalamin (B<sub>12</sub>) level and a complete blood count (CBC) to identify the presence of any type of anemia are recommended for initial testing.<sup>6,16,17</sup> Vitamin B<sub>12</sub> concentrations are generally accurate; however, these tests screen for a deficiency only and will not determine the actual cause. Additionally, not all patients with a deficiency will have hematological manifestations. There are instances where falsely low serum B<sub>12</sub> levels have been associated with the use of oral contraceptives, folate deficiency, and pregnancy.<sup>2,16,17</sup> Falsely high serum B<sub>12</sub> levels might be associated with conditions such as liver disease, renal disease, or myeloproliferative disorders.<sup>16,17</sup> There are conflicting guidelines for determining a deficiency in cobalamin levels, but generally patients with levels less than 200 pg/mL are considered deficient.<sup>2,6,17</sup> Symptomatic patients with levels between 200 and 300 pg/mL might be deficient and supplementation could be beneficial. Symptomatic patients with levels higher than 300 pg/mL are most likely not vitamin B<sub>12</sub>

deficient. If the vitamin B<sub>12</sub> level is normal but your patient's symptoms are consistent with a deficiency, it is appropriate to follow up with methylmalonic acid (MMA) and homocysteine levels. These tests might be more sensitive to identifying a vitamin B<sub>12</sub> deficiency, especially in elderly patients.<sup>6,16,17</sup>

## **Management**

**Supplementation.** Vitamin B<sub>12</sub> supplements are available in several forms: injectable, oral, sublingual, and intranasal.<sup>18</sup> Treatment is determined by the cause of the deficiency, patient preference, and cost.<sup>2,6</sup> Traditional treatment for vitamin B<sub>12</sub> deficiency is intramuscular (IM) administration of cyanocobalamin, a synthetic form of vitamin B<sub>12</sub>.<sup>1,4,19</sup> Cyanocobalamin therapy is usually initiated by administering 1,000 mcg IM every day for 1 or 2 weeks, followed by 1,000 mcg IM every week for 4–6 weeks. Afterward, a maintenance dose of 1,000 mcg IM every month will be needed.<sup>5</sup>

For patients who prefer a different route, high-dose oral treatment is also effective and is increasingly popular.<sup>7</sup> An oral dose of 1,000 to 2,000 mcg per day is usually sufficient.<sup>20</sup> For patients who are unable to actively absorb vitamin B<sub>12</sub> (pernicious anemia), passive absorption in the small bowel still allows an absorption rate of 1%. Therefore, supplementation with 1,000 mcg per day can provide 10 mcg, substantially more than the Recommended Dietary Allowance (RDA) of 2.4 mcg per day.<sup>2,20</sup> When absorption is a concern, IM is the suggested route of treatment due to its higher absorption rate.<sup>1,6</sup> Toxicity risk from dietary vitamin B<sub>12</sub> is unlikely.<sup>1,3,20</sup> Patients with a deficiency who are prescribed very high doses of vitamin B<sub>12</sub> have shown no signs of toxicity.<sup>1,17</sup> It is impossible to consume too much in your diet and any excess is excreted in the urine.<sup>1,17</sup> Patients often choose oral treatment to avoid pain from injections, the

inconvenience of an office visit, and cost.<sup>21,22</sup> The overall goal of supplementation is to determine the level of deficiency and adequately replace vitamin B<sub>12</sub> levels.

**Dietary.** Vitamin B<sub>12</sub> is found mostly in foods of animal origin such as meat and dairy products, including liver, beef, chicken, pork, eggs, milk, cheese,<sup>15</sup> and some varieties of fish.<sup>8</sup> Many breakfast cereals are also fortified with up to 100% of the daily value of vitamin B<sub>12</sub>. The RDA was set at 2.4 µg/d by the Institute of Medicine (IOM) to ensure absorption of 1 µg/d because on average only about 50% of vitamin B<sub>12</sub> is absorbed from food.<sup>7</sup> The RDA for vitamin B<sub>12</sub> in pregnancy is 2.6 µg/day, which is 0.2 µg/day greater than the RDA for non-pregnant women and adolescents. A balanced diet, however, provides somewhere between 7 and 30 µg/day.<sup>3</sup>

Many older adults have difficulty absorbing vitamin B<sub>12</sub>; therefore, the IOM recommends all adults over 50 include B<sub>12</sub>-fortified foods or B<sub>12</sub> supplements in their diet.<sup>1,3,23</sup> Vegans and strict vegetarians, especially those who are pregnant or breastfeeding,<sup>3,11</sup> are also encouraged to consume B<sub>12</sub>-fortified foods such as breakfast cereals, soy milk, and certain soy analog meats,<sup>14</sup> or include supplements in their diets.

Vitamin B<sub>12</sub> has the potential to interact with alcohol and certain medications such as chloramphenicol and colchicines because they affect the way the body breaks down nutrients. Other medications including oral contraceptives, potassium supplements, Metformin, antivirals, and nicotine interfere with the absorption of vitamin B<sub>12</sub>.<sup>3,18,24</sup> Long-term use of proton pump inhibitors (PPIs) are known to reduce vitamin B<sub>12</sub> levels obtained from food but not from supplements; therefore, B<sub>12</sub> levels should be tested because supplementation could be necessary.<sup>18</sup> Early education of patients who use PPIs regarding the potential of a B<sub>12</sub> deficiency can avoid the possibility of an interaction.

***Patient Education.*** Patient and family education should include information regarding vitamin B<sub>12</sub> deficiency, common symptoms, dietary needs, supplementation (including associated costs), and the possible need for lifelong vitamin B<sub>12</sub> replacement.<sup>2,6</sup> Patients could be taught to self-administer cyanocobalamin by injection (if needed), giving them a sense of control and the ability to manage their disorder.<sup>5,6</sup> Patients might also be made aware of available resources that provide helpful information about vitamin B<sub>12</sub> deficiency, including online medical sources and pamphlets. A referral to a dietitian and regular office visits will also assist with proper management and compliance.<sup>6,9</sup>

Dietitians can be helpful for providing guidance to patients with a deficiency on how to increase their vitamin B<sub>12</sub> intake. Patients in each of the high risk groups have unique dietary needs. Working with a dietician can assist a patient in creating a personalized dietary plan to meet individual needs and tastes while boosting vitamin B<sub>12</sub> levels.<sup>6</sup>

### **Conclusion**

Vitamin B<sub>12</sub> deficiency is more common than NPs might realize. It is important to be aware of this condition as a potential diagnosis for the elderly and for patients from high-risk groups. Understanding its pathophysiology, recognizing symptoms, and providing treatment are foundational to early detection, thereby avoiding the potential devastating consequences of untreated vitamin B<sub>12</sub> deficiency.

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