

Review Article

Vitamin B12 and Depression

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Abstract

In previous studies a potential connection between cyanocobalamin (vitamin B12) deficiency and depression has been suggested. Currently in the United States, an acceptable serum B12 reference range is 200-900 pg/mL. However, it is suspected that even serum levels within the lower end of this range can result in symptoms consistent with deficiency, including depression. Thus, supplementation of vitamin B12 may be helpful for the treatment in depressed patients.

Keywords: Cyanocobalamin, vitamin B12, depression, Supplementation

1. Vitamin B12: An Overview

Vitamin B12 is produced by bacteria, and its structure contains cobalt and corrin ring molecules. Cyanocobalamin is the name given to the principal form of vitamin B12 contained in supplements. These two terms are often used interchangeably. Vitamin B12 is attainable from red meats, milk, eggs, fish, and fortified cereals. A deficiency of B12 may occur for a few reasons (NIH -2008):

- Diet: A person may not be getting enough B12 in their diet. Vegans are especially at risk for this.
- Absorption: A person may be consuming an adequate amount of B12, however they may not be absorbing it. This can occur in medical conditions such as Crohn's disease or celiac disease. Intrinsic factor and calcium facilitate absorption of Vitamin B12. Vitamin B12 will not be absorbed from the GI tract if missing these facilitators. Medications that increase the pH of the stomach, such as proton pump inhibitors, may also contribute to malabsorption. Anticonvulsants can decrease its absorption as well.
- Increased utilization: A person's body may also have a higher demand for vitamin B12. This can occur in conditions such as pregnancy, thyrotoxicosis, and liver and kidney disease (NIH -2008).

2. Vitamin B12 is a co-factor in

- Folate absorption
- Synthesis of myelin
- Metabolism of homocysteine
- Production of neurotransmitters.

Therefore, deficiencies may result in anemia, neuropathy, mental disorientation, memory loss, depression, and cardiovascular events. Symptoms of B12 deficiency may include depressed mood, decreased ability to concentrate, decreased energy level, and tingling of the hands and feet (NIH -2008).

The recommended daily allowance of B12 is around 2.4 mcg. There is no upper limit because absorption of B12 is decreased at higher doses. Supplements are available as a nasal spray, tablets, a sub-lingual solution, and in injectable form in 25 mcg to 1000 mcg strengths. Smaller doses are incorporated in some multivitamins (Papakostas et al., 2004).

3. Mechanism of Vitamin B12 in Depression

There are two enzymes which depend on vitamin B12 to work: methionine synthase (MTR) and methylmalonyl coenzyme A mutase (MUT). Decreased activity of either of these enzymes due to decreased levels of vitamin B12 can contribute to development of depression. MTR is responsible for converting 5-methylfolate and homocysteine into tetrahydrofolate and methionine. Methionine is used to make s-adenyl methionine (SAM), which is a precursor of neurotransmitters, and is also an important factor in the production of the myelin sheath. Methylmalonic acid (MMA) is a substrate of MUT, and high levels of MMA can lead to myelin destabilization. Therefore, these two B12 dependent enzymes are partly responsible for healthy neurological activities (NIH -2008).

4. Evidence for a Link between Vitamin B12 and Depression

There is evidence suggesting that symptoms of depression may be linked with low serum levels of B12. The Rotterdam study published in the American Journal of Psychiatry in 2002 examined B12 levels of 278 elderly patients with depressive symptoms of Major Depressive Disorder and Dysthymic Disorder as defined by DSM-IV. Four hundred and one patients without these symptoms or diagnoses were used for comparison. The study found that B12 deficiency did not correlate with depressive symptoms but correlated with diagnosed depressive disorders. The correlation was significant across adjustments made for factors including age, gender, functional disability, and cardiovascular risk factors. The study concluded that patients with low B12 levels were 70% more likely to have a depressive disorder. Furthermore, it concluded that low B12 levels were not associated with a loss of appetite, suggesting that the deficiency may be due to causes other than diet (Tiemeier et al., 2002).

There is also evidence suggesting that higher serum levels of B12 may improve response to antidepressant therapy. In a review article, published in the Journal of Psychopharmacology in 2005, two studies were referenced: one that found B12 levels were higher in patients who responded to treatment with desmethylimipramine (desipramine), and another that found higher RBC folate levels in patients who responded to nortriptyline and sertraline (Coppen and Bolander-Gouaille C, 2005). It was noted that the folate levels could have been influenced by higher levels of B12, since RBC folate synthesis depends on B12 levels.

However, not all evidence is as promising. A 2004 study from the Journal of Clinical Psychiatry examined B12 levels in 55 patients who did not respond to initial treatment with fluoxetine, and were either given a higher dose, switched to desipramine, or given lithium to augment the fluoxetine. Results found that of the 49 patients whose B12 levels were within normal limits, only 19 responded. However, in the six patients with low B12 levels, only one responded (Papakostas et al., 2004).

5. B12 Supplementation: Does it Work?

It has previously been suggested that patients with depression are likely to have low levels of vitamin B12, and that patients with higher levels of B12 may respond better to antidepressant therapy. Could B12 supplementation alone be enough to cure depression?

A small study published in the Journal of Affective Disorders in 1994 explored B12 supplementation in 27 patients with Seasonal Affective Disorder (SAD). Following a two-week washout period, the subjects were randomized to receive either 2 weeks of treatment with oral B12 supplements at a dose of 1.5 mg divided three times a day or placebo. Assessment was done using the 29-item SIGH-SAD score, and no differences were found between the two groups. These findings suggest that B12 supplementation alone may not be enough to treat SAD or other types of depression (Oren et al., 1994). However, larger studies with longer

follow-ups are needed to further explore this.

A study published in August 2008 in the Journal of Clinical Psychiatry looked at supplementation of B12 for prevention of depression in 299 elderly men 75 years and older (Ford AH, et.al., 2008). These participants had mild to moderate depression at most, and some did not have any depressive symptoms at all. The participants were randomized and given multivitamin tablets containing 400 mcg of B12, 2 mg of folic acid, and 25 mg of B6 or a placebo tablet. Depression was measured by the Beck Depression Inventory scoring system at baseline and every six months for two years. Outcomes measured were changes in BDI scores or development of a BDI score >9 , indicating mild depression. The study results found no differences in BDI scores relative to baseline. Patients receiving the supplement were 24% less likely to develop depression (or a score >9), but this difference was found not to be statistically or clinically significant. Overall, the study found that the prevention of development of depressive symptoms was one out of 21 patients. B12 showed similar changes in levels in patients with and without depression. Some disadvantages to this study include that it was underpowered, and that depression was not defined by DSM-IV criteria. Nonetheless, this study suggests that B12 supplementation is not helpful for the prevention of depression, or for improvement of mild to moderate depression, and that its usefulness may be limited to patients who have more severe depression or are treatment-refractory.

5. Conclusion

In conclusion, vitamin B12 is an essential vitamin that has a role in the production of neurotransmitters important for healthy brain function. There is evidence suggesting that severely depressed patients often have low levels of vitamin B12, and that patients with higher levels of B12 may respond better to antidepressant therapy. However, there is little evidence that B12 supplementation alone can cure or prevent depression.

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