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LET'S TAKE BACK YOUR HEALTH—*Starting Now.*

EBOOK

# B12 Deficiency

*by* CHRIS KRESSER

# B12 Deficiency

## A Silent Epidemic With Serious Consequences

What do all of these diseases have in common?

- Alzheimer's, dementia, cognitive decline and memory loss (collectively referred to as "aging")
- Multiple sclerosis (MS) and other neurological disorders
- Mental illness (depression, anxiety, bipolar disorder, psychosis)
- Cardiovascular disease
- Learning or developmental disorders in kids
- Autism spectrum disorder
- Autoimmune disease and immune dysregulation
- Cancer
- Male and female infertility

Answer: they can all mimic the signs and symptoms of vitamin B12 deficiency.

## B12 Deficiency: An invisible epidemic

B12 deficiency isn't a bizarre, mysterious disease. It's written about in every medical textbook and its causes and effects are well-established in the scientific literature.

However, B12 deficiency is far more common than most health care practitioners and the general public realize. Data from the Tufts University Framingham Offspring Study suggest that 40 percent of people between the ages of 26 and 83 have plasma B12 levels in the low normal range – a range at which many experience neurological symptoms. 9 percent had outright deficiency, and 16 percent exhibited "near deficiency". Most surprising to the researchers was the fact that low B12 levels were as common in younger people as they were in the elderly.

That said, B12 deficiency has been estimated to affect about 40% of people over 60 years of age. It's entirely possible that at least some of the symptoms we attribute to "normal" aging – such as memory loss, cognitive decline, decreased mobility, etc. – are at least in part caused by B12 deficiency.

## Why is B12 deficiency so under-diagnosed?

B12 deficiency is often missed for two reasons. First, it's not routinely tested by most physicians. Second, the low end of the laboratory reference range is too low. This is why most studies underestimate true levels of deficiency. Many B12 deficient people have so-called "normal" levels of B12.

Yet it is well-established in the scientific literature that people with B12 levels between 200 pg/mL and 350 pg/mL – levels considered "normal" in the U.S. – have clear B12 deficiency symptoms. Experts who specialize in the diagnosis and treatment of B12 deficiency, like Sally Pacholok R.N. and Jeffery Stewart D.O., suggest treating all patients that are symptomatic and have B12 levels less than 450 pg/mL. They also recommend treating patients with normal B12, but elevated urinary methylmalonic acid (MMA), homocysteine and/or holotranscobalamin (other markers of B12 deficiency).

In Japan and Europe, the lower limit for B12 is between 500-550 pg/mL, the level associated with psychological and behavioral manifestations such as cognitive decline, dementia and memory loss. Some experts have speculated that the acceptance of higher levels as normal in Japan and the willingness to treat levels considered "normal" in the U.S. explain the low rates of Alzheimer's and dementia in that country.

## What is vitamin B12 and why do you need it?

Vitamin B12 works together with folate in the synthesis of DNA and red blood cells. It's also involved in the production of the myelin sheath around the nerves, and the conduction of nerve impulses. You can think of the brain and the nervous system as a big tangle of wires. Myelin is the insulation that protects those wires and helps them to conduct messages.

Severe B12 deficiency in conditions like pernicious anemia (an autoimmune condition where the body destroys intrinsic factor, a protein necessary for the absorption of B12) used to be fatal until scientists figured out death could be prevented by feeding patients raw liver (which contains high amounts of B12). But anemia is the final stage of B12 deficiency. Long before anemia sets in, B12 deficiency causes several other problems, including fatigue, lethargy, weakness, memory loss and neurological and psychiatric problems.

B12 deficiency occurs in four stages, beginning with declining blood levels of the vitamin (stage I), progressing to low cellular concentrations of the vitamin (stage II), an increased blood level of homocysteine and a decreased rate of DNA synthesis (stage III), and finally, macrocytic anemia (stage IV).

# Why is B12 deficiency so common?

The absorption of B12 is complex and involves several steps – each of which can go wrong. Causes of B12 malabsorption include:

- intestinal dysbiosis
- leaky gut and/or gut inflammation
- atrophic gastritis or hypochlorhydria (low stomach acid)
- pernicious anemia (autoimmune condition)
- medications (especially PPIs and other acid-suppressing drugs)
- alcohol
- exposure to nitrous oxide (during surgery or recreational use)

This explains why B12 deficiency can occur even in people eating large amounts of B12-containing animal products. In fact, many of my patients that are B12 deficient are following a Paleo diet where they eat meat 2-3 times a day.

**In general, the following groups are at greatest risk for B12 deficiency:**

- vegetarians and vegans
- people aged 60 or over
- people who regularly use PPIs or acid suppressing drugs

- people on diabetes drugs like metformin
- people with Crohn's disease, ulcerative colitis, celiac or IBS
- women with a history of infertility and miscarriage

## Note to vegetarians and vegans: B12 is found ONLY in animal products

B12 is the only vitamin that contains a trace element (cobalt), which is why it's called cobalamin. Cobalamin is produced in the gut of animals. It's the only vitamin we can't obtain from plants or sunlight. Plants don't need B12 so they don't store it.

A common myth amongst vegetarians and vegans is that it's possible to get B12 from plant sources like seaweed, fermented soy, spirulina and brewers yeast. But plant foods said to contain B12 actually contain B12 analogs called cobamides that block intake of and increase the need for true B12.

This explains why studies consistently demonstrate that up to 50% of long-term vegetarians and 80% of vegans are deficient in B12.

The effects of B12 deficiency on kids are especially alarming. Studies have shown that kids raised until age 6 on a vegan diet are still B12 deficient even years after they start eating at least some animal products. In one study, the researchers found:

> *…a significant association between cobalamin [b12] status and performance on tests measuring fluid intelligence, spatial ability and short-term memory" with formerly vegan kids scoring lower than omnivorous kids in each case.*

The deficit in fluid intelligence is particularly troubling, the researchers said, because:

> *…it involves reasoning, the capacity to solve complex problems, abstract thinking ability and the ability to learn. Any defect in this area may have far-reaching consequences for individual functioning.*

I recognize that there are many reasons why people choose to eat the way they do, and I respect people's right to make their own choices. I also know that, like all parents,

vegetarians and vegans want the best for their children. This is why it's absolutely crucial for those that abstain from animal products to understand that there are no plant sources of B12 and that all vegans and most vegetarians should supplement with B12. This is especially important for vegetarian or vegan children or pregnant women, whose need for B12 is even greater than adults.

## Treatment of B12 deficiency

One of the greatest tragedies of the B12 epidemic is that diagnosis and treatment is relatively easy and cheap – especially when compared to treatment of the diseases B12 deficiency can cause. A B12 test can be performed by any laboratory, and should be covered by insurance. If you don't have insurance, you can order it yourself from a lab like DirectLabs.com for $60.

As always, adequate treatment depends on the underlying mechanism causing the problem. People with pernicious anemia or inflammatory gut disorders like Crohn's disease are likely to have impaired absorption for their entire lives, and will likely require B12 injections indefinitely. This may also be true for those with severe B12 deficiency causing neurological symptoms.

Some recent studies have suggested that high dose oral or nasal administration may be as effective as injections for those with B12 malabsorption problems. However, most B12 experts still recommend injections for people with pernicious anemia and advanced B12 deficiency involving neurological symptoms.

Cyanocobalamin is the most frequently used form of B12 supplementation in the US. But recent evidence suggests that hydroxycobalamin (frequently used in Europe) is superior to cyanocobalamin, and methylcobalamin may be superior to both – especially for neurological disease.

Japanese studies indicate that methylcobalamin is even more effective in treating the neurological sequelae of B12 deficiency, and that it may be better absorbed because it bypasses several potential problems in the B12 absorption cycle. On top of that, methylcobalamin provides the body with methyl groups that play an role in various biological processes important to overall health.

If you suspect you have B12 deficiency, the first step is to get tested. You need an accurate baseline to work from. If you are B12 deficient, the next step is to identify the mechanism causing the deficiency. This is something you'll probably need help with from a medical practitioner. Once the mechanism is identified, the appropriate form (injection, oral, sublingual or nasal) of supplementation, the dose and the length of treatment can be selected.

So, next time you or someone you know is "having a senior moment", remember: it might not be "just aging". It could be B12 deficiency.

## What Everyone (Especially Vegetarians) Should Know About B12 Deficiency

One of the biggest problems with diagnosing B12 deficiency is that the conventional serum B12 test that most doctors run only picks up a small fraction of people who are actually B12 deficient. This test measures the total amount of B12 in the blood, and does not rule out functional B12 deficiency. More sensitive markers for B12 deficiency are now available, including methylmalonic acid (MMA) and holotranscobalamin II (holo-TC). MMA is converted to succinic acid via an active-B12 dependent enzyme, so if MMA levels are high, it suggests that active B12 is lacking. Holotranscobalamin II is composed of vitamin B12 attached to transcobalamin, and it represents the biologically active part of B12 that can actually be delivered to the cells and perform all of the functions of B12. Studies using these newer methods report much higher levels of deficiency than studies using only serum B12.

For example, one review using serum B12 indicated that 52% of vegans and 7% of vegetarians are B12 deficient. But a study using the more sensitive techniques found much higher rates of deficiency: **68% for vegetarians and 83% of vegans**, compared to just 5% of omnivores. That's a huge, game-changing difference. It means that conventional testing is missing 61% of vegetarians and 31% of vegans that are B12 deficient. This is especially important because B-12 depletion can take years to become clinically evident (i.e. deficiency sets in long before obvious symptoms appear), and some of the more serious effects of B12 deficiency (such as nerve damage) are irreversible.

Although rates of B12 deficiency are much higher in vegetarians and vegans than in omnivores, that doesn't mean it's rare in omnivores. According to the study above, approximately 1 in 20 omnivores are B12 deficient. In my practice I'd estimate the rate at closer to 1 in 15, possibly because I see a lot of people with gut problems and that is one of the risk factors for B12 deficiency. Other risk factors include age (people 60 or older), present or past use of acid-suppressing drugs or other medications like metformin and women with a history of miscarriage and infertility.

Frankly, I'm amazed that this very serious problem doesn't get more attention in the media. As Sally Pacholok and Jeffrey Stuart point out in their book Could It Be B12: An Epidemic of Misdiagnoses:

> *Over-diagnosis of B12 deficiency is essentially innocuous [because B12 is so safe to supplement with]; but…'missed diagnosis is quite clearly a matter of great gravity, particularly since the risk of formidable devastation from neurologic damage that results from uncorrected cobalamin deficiency is preventable.'*

## The importance of early diagnosis

Researchers now recognize four categories of B12 deficiency:

- Stage I & II: plasma and cell stores of B12 become depleted and the concentration of holotranscobalamin II is reduced.
- Stage III: functional B12 imbalance characterized by elevated homocysteine and urinary MMA concentrations in the blood.
- Stage IV: clinical signs of B12 deficiency become evident.

As you can see, signs like macrocytic anemia and symptoms like peripheral neuropathy or brain fog do not appear until the final stage of B12 deficiency. By then, in the case of the neurological symptoms, it may be too late to reverse them. This makes early diagnosis crucial.

Of all of the available markers I mentioned above, holo-TC is considered to be the most sensitive. It can detect B12 deficiency in Stages I & II, whereas urinary MMA and homocysteine typically don't become elevated until Stage III. Unfortunately, holo-TC is not yet widely available. Quest Diagnostics has recently begun to offer it, though, and it

is one of the largest national laboratories so your doctor should be able to order it if you ask. *[Update: although Quest lists it on their website, they apparently do not offer it at any Quest location in US as of 1-18-13.]*

There are two ways to have MMA measured: in the serum, and in the urine. Each has advantages and disadvantages. Some experts believe that urinary MMA is superior to serum MMA as a marker — possibly because it is more concentrated in the urine than the blood. However, elevations in urinary MMA can also be caused by kidney dysfunction. (1, 2) On the other hand, serum MMA can be elevated in the presence of intestinal bacterial overgrowth. Therefore, which test you choose should depend on your health status. If there's any question of impaired kidney function, serum MMA would be a better choice. If you have or think you may have SIBO or gut dysbiosis, urinary MMA would be the better choice. Quest, Labcorp and many other labs offer both serum or urinary MMA, so you shouldn't have any problem getting it provided your doctor will order it. Note that you need to be fasting for the urinary MMA to get an accurate result.

If you can't get either of these tests, you can order the standard serum B12 test yourself from DirectLabs.com or through your doctor. However, in that case you need to use a different range than what the lab provides. Although most labs define deficiency at <200 pg/mL, it is well documented that many people experience signs and symptoms of B12 deficiency at levels between 200 pg/mL and 350 pg/mL.

Also, be aware that a **high serum B12 does not necessarily rule out functional/active B12 deficiency.** In fact, I have come to view a high serum B12 in the absence of supplementation as a potential red flag for active B12 deficiency.

# If you suspect you have B12 deficiency

The first step is to get a holo-TC and/or urinary MMA test. If either of them are abnormal, you should immediately take steps to increase your B12 levels. There are two ways to do this:

1. Eat B12-rich foods.
2. Supplement.

B12 is the only vitamin that contains a trace element (cobalt), which is why it's called cobalamin. Cobalamin is produced in the gut of animals. It's the only vitamin we can't obtain from plants or sunlight. Plants don't need B12 so they don't store it. B12 is found exclusively in animal foods, such as liver, clams, oysters, mussels, fish eggs, octopus, fish, crab and lobster, beef, lamb, cheese and eggs.

A common myth amongst vegetarians and vegans is that it's possible to get B12 from plant sources like seaweed, fermented soy, spirulina and brewers yeast. But plant foods said to contain B12 actually contain B12 analogs called cobamides that block intake of and increase the need for true B12. My intention here is not to bash vegetarian and vegan diets. (I was a macrobiotic vegan myself at one point, for crying out loud!)

I recognize that there are many reasons why people choose to eat the way they do, and I respect people's right to make their own choices. I also know that, like all parents, vegetarians and vegans want the best for their children. This is why it's crucial for those that abstain from animal products to understand that there are no plant sources of B12 and that all vegans and most vegetarians should supplement. This is especially important for vegetarian or vegan children or pregnant women, whose need for B12 is even greater than adults. In addition, omnivores that are low in B12 despite eating a diet rich in animal foods that contain B12 should also supplement.

# Supplementing with B12

Cyanocobalamin is the most frequently used form of B12 supplementation in the US. But recent evidence suggests that hydroxycobalamin (frequently used in Europe) is superior to cyanocobalamin, and methylcobalamin may be superior to both – especially for neurological disease. (3, 4 p. 225) This is probably because methylcobalamin bypasses several problems in the B12 absorption cycle and doesn't need to be decyanated or reduced to the (+1) state (the only state that can cross the blood-brain barrier). On top of that, methylcobalamin provides the body with methyl groups that play a role in various biological processes important to overall health.

A general approach to B12 supplementation might include 1,000 mcg (1 mg) of sublingual methylcobalamin — Jarrow Formulas Methyl-B12 is a good choice — along with co-

factors like folate (Solgar Folate 800 Mcg 1x/d), potassium (Natures Way Potassium 99mg 3x/d) and trimethylglycine/TMG (Jarrow 500mg 1x/d).