

## Vitamin B12

It is also known as cobalamin. It comes in different forms (cyanocobalamin, methylcobalamin, and hydroxycobalamin). Cyano- is generally advised as being the most stable, with the exception for people who have kidney disease where the methyl- is better. Some people have a genetic mutation called MTHFR (that can be discovered through genetic testing) and they might do better with the methyl form of B-12 as well, but this is not a clear cut issue. Some say that genetic testing such as through 23 & Me is the way to go to identify which form to use. Based on your genetic profile 1, 2 or all 3 forms may be best. Others say that methyl- is the form to use since the other two have to be converted into it.

It is available in pill form, along with nasal, injection, lozenges, and sublingual. Anything that is swallowed and is 'more than a pill' may have sugar substitutes in it like mannitol, sorbitol or sucralose which in some people cause gas, bloating or diarrhea especially if you take more than one at a time.

B12 is part of a 'complex' of B vitamins and taking them together will be better as to absorption. Whether sublingual is best is debated. Some say it is because it gets into the bloodstream and does not have to deal with gut absorption issues. Others suggest sublingual is not necessarily better. Use of IV B12 is also thought to be better for the same reason of getting into the bloodstream directly, but people may not like having to go to a doctor to get a shot.

### What it does:

- ❖ helps with red blood cell formation and prevents anemia (in a B12 deficiency state the red blood cells become larger and more oval in shape and are unable to move from the bone marrow into the bloodstream at a normal rate, causing megaloblastic anemia, leading to weakness and fatigue. Long term effects of this issue with the bone marrow can lead to damage in organs like the brain and heart.)
- ❖ it may prevent birth defects (B12 deficiency in the early stages of pregnancy may increase the risk of birth defects like neural tube defects, along with contributing to increased risk of premature birth or miscarriage. One study found that expecting mothers having a B12 level lower than 250 mg/dl were three times more likely to give birth to a child with birth defects, vs. more normal levels of B12 (Pediatrics, March 2009).
- ❖ it may support bone health and prevent osteoporosis
- ❖ it may reduce the risk of macular degeneration (B12 may lower homocysteine, an amino acid, and elevated levels of homocysteine has been associated with increased risk of macular degeneration. Supplementing with B12, folic acid, and B6 may reduce the risk (Archives of Internal Medicine, Feb. 2009)
- ❖ it may improve mood and symptoms of depression. B12 is involved with the synthesizing and metabolism of serotonin which is a neurotransmitter involved with regulating mood (e.g. drugs like Prozac work on serotonin). Consequently, low B12 may lead to lower serotonin production which then may cause depressed mood. (One study found that B12

deficiency was associated with twice the risk of severe depression, with 27% of severely depressed women age 65 or older being deficient, along with 17% of the mildly depressed, and about 15% of the nondepressed (American Journal of Psychiatry, "Vitamin B(12) deficiency and depression in physically disabled older women: epidemiological evidence from the Women's Health & Aging Study" BW Penninx, et al, May 2000).

- ❖ it may help prevent loss of brain cells. B12 deficiency has been associated with memory loss especially in older adults, and this means it may prevent brain atrophy which is associated with dementia. One study on people with early-stage dementia found that B12 plus omega-3 supplements slowed mental decline (Journal of Alzheimer's Disease, Jan. 6 2016). Another study found that in people with B12 just on the low side of normal poor memory may result (American Journal of Clinical Nutrition, April 2016).
- ❖ may improve energy level for those who are deficient in B12. One of the most common early signs of B12 deficiency is fatigue or a lack of energy.
- ❖ promotes healthy hair, skin and nails. Low B12 levels cause various skin problems including hyperpigmentation, nail discoloration, hair changes, vitiligo (patchy loss of skin color), and cracked or inflamed corners of the mouth.

Symptoms of B12 deficiency include:

- ❖ depression
- ❖ confusion
- ❖ memory problems
- ❖ fatigue
- ❖ constipation
- ❖ loss of appetite
- ❖ weight loss
- ❖ numbness and tingling in the hands and feet
- ❖ balance difficulties
- ❖ anemia (symptoms of which may include fatigue, shortness of breath, irregular heartbeat, sore mouth or tongue, pale or yellowing skin, diarrhea, menstrual problems)
- ❖ paranoia
- ❖ hallucinations
- ❖ muscle cramps; nighttime leg cramps and spasms
- ❖ in infants, the most common symptoms of low B12 (most commonly due to breastfeeding and maternal deficiency in the vitamin) were:
  - periods of no breathing or small breaths (apnea)
  - motor seizures
  - staring spells (absence)
  - tremors
  - irritability
  - poor muscle tone
  - abnormal eye contact

Who is at risk of deficiency of B12:

- ❖ being over the age of 60 (some say over the age of 50, with one estimate offering that about half of those over age 50 fall short of B12) in that such people have reduced stomach acid which makes for a reduction in B12 absorption
- ❖ having GI disorders like Crohn's or celiac disease
- ❖ having GI surgery like bariatric or bowel resection surgery
- ❖ use of acid-blocking drugs (PPI's, e.g. Prilosec), which some say may be the most common cause of deficiency
- ❖ vegetarians and vegans
- ❖ alcohol and drug abusers
- ❖ people recovering from surgery or burns
- ❖ those with Parkinson's tend to have lower levels but may still be within the normal range. Those with lower B12 levels have been linked to more Parkinson's progression, greater cognitive impairment, and increased risk of neuropathy. Supplementing with B12 and B6 may help reverse symptoms of neuropathy in Parkinson's with low levels of those vitamins associated with levodopa treatment.
- ❖ long term use of Metformin (such as for diabetes) is associated with increased risk of B12 deficiency. It is advised to check B12 levels every 2-3 years even if they don't show signs of deficiency.

Drugs that can reduce B12 levels in the body include:

Acid blockers

- ❖ Cimetidine/Tagamet
- ❖ Esomeprazole/Nexium
- ❖ Famotidine/Pepcid
- ❖ Lansoprazole/Prevacid
- ❖ Nizatidine/Axid
- ❖ Omeprazole/Prilosec
- ❖ Pantoprazole/Protonix
- ❖ Rabeprazole/Aciphex
- ❖ Ranitidine/Zantac

Antacids

- ❖ Aluminum & magnesium hydroxide/Maalox, Mylanta
- ❖ Aluminum carbonate gel/Basaljel
- ❖ Aluminum hydroxide/Amphojel, AlternaGEL
- ❖ Calcium carbonate/Tums, Rolaids
- ❖ Magnesium hydroxide/Milk of Magnesia
- ❖ Sodium bicarbonate/Alka-Seltzer, baking soda

Antibiotics (these are just some examples)

- ❖ Amoxicillin/Amoxil
- ❖ Azithromycin/Z-pak

- ❖ Cefaclor/Celor
- ❖ Cefdinir/Omnicef
- ❖ Cephalexin/Keflex
- ❖ Ciprofloxacin/Cipro
- ❖ Clarithromycin/Biaxin
- ❖ Dicloxacillin/Dynapen
- ❖ Doxycycline/Doryx
- ❖ Erythromycin/EES
- ❖ Isoniazid/INH
- ❖ Levofloxacin/Levaquin
- ❖ Minocycline/Minocin
- ❖ Sulfamethoxazole and trimethoprim/Bactrim sepra
- ❖ Tetracycline/Sumycin

#### Anticonvulsants

- ❖ Phenobarbital (Solfoton)
- ❖ Phenytoin/Dilantin (space supplement at least 2 hours away from the medication)
- ❖ Primidone/Mysoline

#### Antigout

- ❖ Colchicine/Colcrys

#### Antivirals

- ❖ Foscarnet/Foscavir
- ❖ Lamivudine/Epivir
- ❖ Stavudine/Zerit
- ❖ Zidovudine, AZT/Retrovir
- ❖ Zidovudine and Lamivudine/Combivir

#### Blood pressure

- ❖ Methyldopa/Aldomet

#### Cholesterol

##### Fibrate:

- ❖ Clofibrate/Atromid-S
- ❖ Ezetimibe/Zetia
- ❖ Fenofibrate/Tricor
- ❖ Gemfibrozil/Lopid

##### Bile acid sequestrant:

- ❖ Cholestyramine resin/Qustran
- ❖ Colestipol/Colestid
- ❖ Colesevelam/Welchol

Diabetes

- ❖ Glimepiride/Amaryl
- ❖ Glipizide/Glucotrol
- ❖ Glyburide/Diabeta, Glynase, Micronase
- ❖ Glyburide and metformin/Glucoavance
- ❖ Metformin/Fortamet, Glucophage, Glumetza, Riomet
- ❖ Metformin and sitagliptin/Janumet
- ❖ Pioglitazone/Actos
- ❖ Rosiglitazone/Avandia

Hormone replacement therapy/oral contraceptives

- ❖ Estradiol/Activella, Climara, CombiPatch, Estraderm, Estring, EstroGel, Menostar, and others)
- ❖ Estrogen-containing drugs (Estrace, Femring)
- ❖ Estrogens conjugated (Premphase, Prempro)
- ❖ Ethinyl estradiol (found in many birth control pills)
- ❖ Norethindrone/Aygestin)

Nonsteroidal aromatase inhibitors for breast cancer

- ❖ Anastrozole/Arimidex

Parkinson's

- ❖ Levodopa & carbidopa/Sinemet

Psychiatric

- ❖ Chlorpromazine/Thorazine
- ❖ Fluphenazine/Prolixin
- ❖ Haloperidol/Haldol
- ❖ Thioridazine/Mellaril

Selective estrogen receptor modulators for breast cancer

- ❖ Raloxifene/Evista
- ❖ Tamoxifen/Nolvadex
- ❖ Toremifene/Fareston

Miscellaneous

- ❖ Alcohol
- ❖ Estrogen dominance hypochlorhydria (low stomach acid)
- ❖ Infection with H. pylori bacteria
- ❖ Potassium supplements and drugs (Micro-K, Slow-K)

How common B12 deficiency is debated, meaning there is a wide spread in estimates. One study suggested that

- ❖ 40% of people between ages 26-83 have B12 levels in the low to normal range – which is where neurological symptoms are experienced.
- ❖ 9% had outright deficiency
- ❖ 16% had ‘near deficiency’
- ❖ B12 levels were low in younger people as often as they were in the elderly
- ❖ estimates that B12 deficiency creates some adverse symptoms in 40% of people over the age of 60. i.e. What we consider ‘normal aging’ like memory loss and cognitive decline may be in part due to B12 deficiency.

One of the reasons that deficiency rates is hard to determine is that it is often missed because it is not routinely tested for by doctors. Plus, the lower end of what is considered a normal level is thought to be too low, meaning a person can be labeled as ‘within the normal range’ when they should be recognized as being deficient.

The scientific literature has shown that B12 levels between 200-350 pg/ml which is considered ‘normal’ actually have deficiency symptoms. Experts who specialize in B12 deficiency therefore suggest that levels below 450 pg/ml be considered deficient and treated. Japan and Europe have a lower limit of B12 at 500-550 pg/ml. It is thought that this may explain why such classification and treatment for low levels explain why there is less Alzheimer’s and dementia in places like Japan.

High doses of B12 are generally not considered to be toxic. e.g. One study called HOPE 2 gave 1 mg for 5 years and did not find serious adverse consequences.

However, in pregnant women, B12 blood levels above 813 pg/mL had a 3 times higher risk of autism in their offspring, and it was 17.6 times higher when both B12 and folate were excessive. Other research on 4860 people found that for type 2 diabetics the safest range was 369.1-506.0 pg/ml. Below 369.1 there was a 74% increased risk for cardiovascular death. Rates of 506.1-703.4 had a 79% increased risk of death. And above 703.5 there was a 132% increased risk of death too. i.e. Goldilocks levels, of not too much, not too little but just right are best. ([JAMA Network Open](#), “Associations of serum folate and Vitamin B12 levels with cardiovascular disease mortality among patients with type 2 diabetes” Yujie Liu et al, 1/31/2022.)

For people in general toxic levels of B12 might lead to problems like dizziness, anxiety, headache, nausea, and vomiting. Swelling in the cheeks, tongue and throat are possible too, along with problems swallowing and breathing are other symptoms of such toxicity. Emergency medical contact should be initiated under such circumstances. One other possible cause of elevated B12 levels is liver problems. Another potential cause of toxicity is for people with the MTHFR genetic defect that impacts methylation leading to B12 to ‘pool’ in one’s system because it is not being broken down properly. Use of methylated B12 and folate are advised for people with such a genetic trait. There is also some research suggesting that high B12 levels are associated with increased risk of cancer such as in the liver and pancreas.

Then there is the issue of how B12 is tested and which form is being assessed. Measuring the vitamin in one's blood is said to be less accurate due to various factors. These can include being on oral contraceptives, having low folic acid levels, pregnancy, and genetic factors. The most accurate way to assess for B12 is through looking at an enzyme called methylmalonic acid (MMA). If B12 levels are low MMA builds up in the blood and becomes high. The test is said to be 99% accurate. The test can lose accuracy for people with kidney disease, thyroid disease, or bacterial overgrowth in the intestine (SIBO). Pregnancy can also impact it.

Another issue is that there are two forms of B12: active and inactive. The active form (also called holoTC, an abbreviation for holotranscobalamin) is what your body can digest, absorb and use right away and it is found in animal-based foods. Inactive B12 may be found in plant-based foods like seaweed and nutritional yeast. It is not well absorbed, and it may interfere with the body's ability to use the active B12.

Tests can measure total B12 which means both the active and inactive form. Or only active B12 can be measured. The normal range for Total B12 according to some is between 200-1100 ng/l. Active B12 levels are said to fall between 20-134 ng/l. The inactive form might represent as much as 80% of the total B12, so although the result may fall in the normal range you would still be deficient in what your body actually needs, the active form.

Another way to measure B12, sort of, is through routine blood work, the CBC. There is something called MCV (mean corpuscular volume) which reflects the size of your red blood cells. As B12 levels fall red blood cells start to grow bigger. And bigger is not better. A MCV greater than 90 or 92 might be used as an early marker of B12 deficiency. Another test that may indicate B12 deficiency is homocysteine. For this chemical to be broken down B12 is required, so if you are deficient in B12 homocysteine levels will rise. High homocysteine levels increase the risk of heart disease.

One other issue to be aware about blood tests for B12 is what was offered in the opening paragraph of this document, namely the MTHFR defect and if you have it whether or not you can utilize cyanocobalamin effectively.

There is disagreement about which plant-based foods have active forms of B12. e.g. Some say that seaweed or algae like chlorella or nori are good, and others say they are low or unreliable and may vary between brands. What is considered the safest source of B12 for vegetarians and vegans is a supplement. Symptoms of B12 deficiency may not show up for some number of years of inadequate intake but damage is still being done such as to the nervous system. So an ounce of prevention is being recommended.

#### Sources of B12:

- ❖ beef
- ❖ pork
- ❖ ham
- ❖ poultry

- ❖ lamb
- ❖ fish, especially haddock and tuna
- ❖ dairy (e.g. milk, cheese, yogurt)
- ❖ some nutritional yeast products
- ❖ eggs
- ❖ some soy milk
- ❖ some breakfast cereals that are fortified with it

Dosages of cobalamin (mcg/day; different researchers offer different figures, these are on the higher side):

	Daily dose	Multiple dose per day	Weekly dose
6 months – 3 years	5	1 mcg x2	--
4-10 years	25	2 mcg x2	--
Kids 11 on up	50	2 mcg x3	1000 mcg x2
18-64 years	50		
65+ years	1000		
Pregnancy	50 (25 x2/day is better for bioavailability)	2 mcg x3	1000 mcg x2
Lactating mothers	50	2 mcg x3	1000 mcg x2

B12 is absorbed very poorly. e.g. To absorb 3.5 mcg one may need to take a single dose of about 250 mcg, so there's the theoretical of how much you should get, and the practical. To get 3.5 mcg/day taken in a single weekly dose would require about 2,500 mcg. Ultimately, the only way to know how well your body is absorbing B12 is to get blood tests and modify the intake based on what is found. Folate (folic acid) enhances B12 absorption. However, too much folic acid can mask a B12 deficiency which can lead to nerve damage.

B12 crosses the placenta during pregnancy and is present in breast milk. Mothers who breastfeed and consume no animal products may have very limited amounts of B12 and can become deficient within months of a baby being born. If infants remain B12 deficient it can result in severe and permanent neurological damage. It is therefore advised that B12 supplementation be used by vegans and lacto-ovo vegetarians during both pregnancy and breastfeeding to insure that babies get enough of the vitamin. Strict vegetarians and vegans should talk to their pediatrician about B12 supplementation.

#### Interactions:

B12 has the potential to interact with meds and discussion with family doctors is advised. Interactions include (but others may exist):

- ❖ Metformin may reduce absorption of B12, and limited research suggests this may impact 10-30% of patients using the drug. One study found that type 2 diabetics using Metformin for 4.3 years had significantly decreased B12 level and raised the risk of it reaching deficiency levels.



- ❖ Vitamin C, copper and thiamine taken with B12 can degrade it. Therefore, taking B12 through use of a multivitamin is not suggested. On the other hand chewing a B12 supplement can greatly boost the level beyond taking the same dose without chewing.

Excess B12 can be antagonistic to vitamin B1 and C, along with magnesium, potassium, and zinc.

Some of the drugs that B12 (cyanocobalamin) can interact with (**red indicates serious, blue moderate**, black milder interactions) include:

- ❖ aminosalicylic acid: it may decrease absorption of B12. It should rarely lead to a significant deficiency of the vitamin.
- ❖ **arsenic trioxide**: use of the vitamin with the drug may increase the risk of an irregular heart rhythm that can be serious and possibly life-threatening. Low potassium levels can result from use of the vitamin, and that can lead to an irregular heartbeat, as well as problems like muscle weakness, paralysis, breathing and swallowing difficulties. A dose adjustment may be needed. Tell your doctor if you have problems with nausea, vomiting, constipation, abdominal cramping, confusion, dizziness, lightheadedness, fainting, muscle weakness, muscle cramps, numbness, tingling, rapid pulse, chest pain, or swelling the legs or feet, all of which can be signs of low potassium.
- ❖ **chloramphenicol**: it may interfere with the vitamin. Contact your doctor if your symptoms worsen or changes.
- ❖ cimetidine: it may interfere with the vitamin's absorption. Use of other forms of intake of the vitamin (e.g. sublingual, nasal) may be preferable.
- ❖ dexlansoprazole: it may interfere with the vitamin's absorption. Use of other forms of intake of the vitamin (e.g. sublingual, nasal) may be preferable.
- ❖ esomeprazole: it may interfere with the vitamin's absorption. Use of other forms of intake of the vitamin (e.g. sublingual, nasal) may be preferable.
- ❖ famotidine: it may interfere with the vitamin's absorption. Use of other forms of intake of the vitamin (e.g. sublingual, nasal) may be preferable.
- ❖ lansoprazole: it may interfere with the vitamin's absorption. Use of other forms of intake of the vitamin (e.g. sublingual, nasal) may be preferable.
- ❖ nizatidine: it may interfere with the vitamin's absorption. Use of other forms of intake of the vitamin (e.g. sublingual, nasal) may be preferable.
- ❖ omeprazole: it may interfere with the vitamin's absorption. Use of other forms of intake of the vitamin (e.g. sublingual, nasal) may be preferable.
- ❖ pantoprazole: it may interfere with the vitamin's absorption. Use of other forms of intake of the vitamin (e.g. sublingual, nasal) may be preferable.
- ❖ potassium chloride: it may interfere with the vitamin's absorption. Use of other forms of intake of the vitamin (e.g. sublingual, nasal) may be preferable.
- ❖ rabeprazole: it may interfere with the vitamin's absorption. Use of other forms of intake of the vitamin (e.g. sublingual, nasal) may be preferable.
- ❖ ranitidine/bismuth citrate: it may interfere with the vitamin's absorption. Use of other forms of intake of the vitamin (e.g. sublingual, nasal) may be preferable.

**Low potassium levels** can result leading potentially to death. Monitoring and correction of potassium levels is needed during B12 therapy. Tell your doctor if you have problems with nausea, vomiting, constipation, abdominal cramping, confusion, dizziness, lightheadedness, fainting, muscle weakness, muscle cramps, numbness, tingling, rapid pulse, chest pain, or swelling the legs or feet, all of which can be signs of low potassium.

**Optic nerve problems** in Leber's disease can have the vitamin cause severe and rapid optic nerve atrophy.

**Malabsorption syndrome** can lead to a decrease in how much of the vitamin is absorbed.

**Renal impairment** - cyanocobalamin contain aluminum that may be toxic if kidney problems are present. Premature babies are especially at risk. Caution and monitoring are recommended.