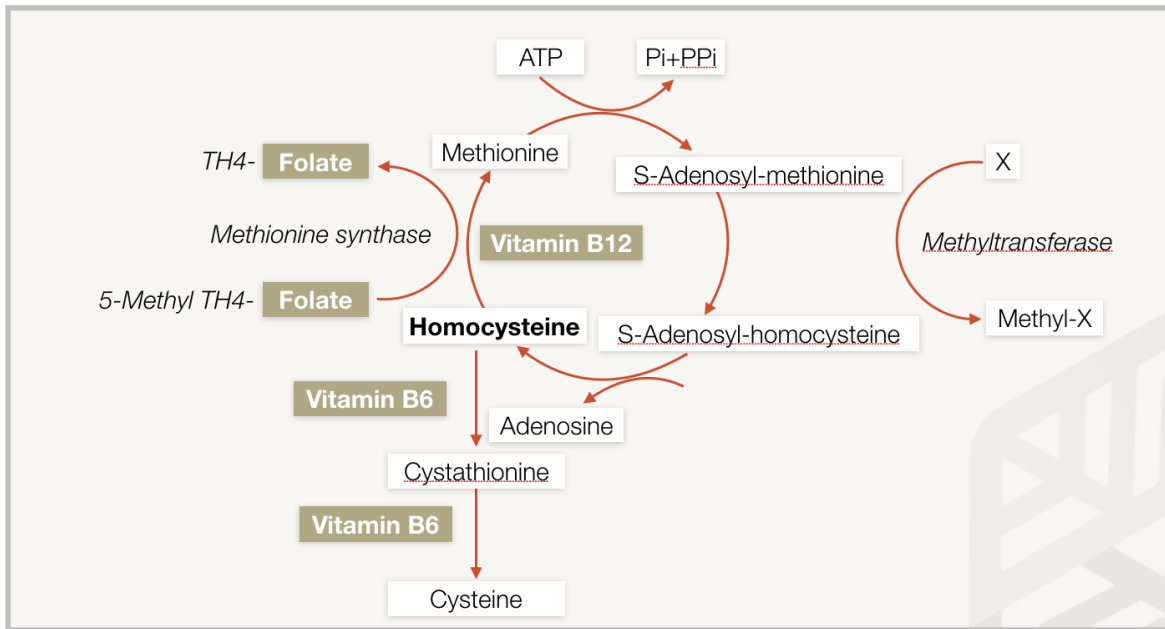


Blood Chem Vitamin B12 Deficiency Review

Vitamin B12 works 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.
- Methylcobalamin is a cofactor for methionine synthase. This enzyme is required for the synthesis of the amino acid methionine from homocysteine in the methylation cycle. Methionine in turn is required for the synthesis of S-adenosylmethionine, a methyl group donor used in many biological methylation reactions, including the methylation of a number of sites within DNA, RNA, and proteins.

VITAMIN B12 AND HOMOCYSTEINE METABOLISM



- B12 also plays a role in energy production.
- New research suggests that B12 may play a role in nitric oxide production and may explain why B12 supplementation has been shown to reduce the severity of autoimmune conditions.
- 40 percent of Americans have low-normal B12 levels.
- 40 percent of people over 60 are B12 deficient, which can mimic the signs and symptoms of diseases that are commonly associated with aging such as Alzheimer's, dementia, cognitive disorders, multiple sclerosis, Parkinson's, and other neurological problems; mental illnesses such as depression and anxiety; cardiovascular disease; cancer; and low libido.

- Serum B12. “Normal” isn’t always normal, as the scientific literature has shown that people with B12 levels between 200 and 350, normal levels in the U.S., may exhibit clear B12 deficiency symptoms and does not rule out functional B12 deficiency.

MORE SENSITIVE MARKERS OF B12 DEFICIENCY

- Methylmalonic Acid (MMA)
- Homocysteine
- Holotranscobalamin-2, or holoTC

CAUSES OF B12 DEFICIENCY

- Inadequate intake
- Intestinal malabsorption due to low stomach acid or GI disorder.
- Pernicious anemia, an autoimmune condition resulting in the destruction of parietal cells that produce intrinsic factor or antibodies to intrinsic factor itself. Intrinsic factor is required to absorb B12.
- Atrophic gastritis, often caused by H. pylori infection in the elderly
- Pancreatic enzyme insufficiency
- Alcoholism, which reduces the absorption of B12 in the terminal ileum.

POPULATIONS AT RISK

- Vegetarians and vegans. B12 is only found in animal products
 - I recommend all vegetarian and vegans, especially children or pregnant women supplement with B12.
- The elderly, who may have low stomach acid due to H. pylori infection and chronic PPI use.
- Those with digestive disorders that lead to malabsorption; for example, celiac and Crohn’s since B12 is absorbed in the terminal ileum.
- Women with frequent or recurrent miscarriage or infertility.
- Those with genetic polymorphisms affecting B12 assimilation and metabolism. I recommend using functional B12 markers over genetic testing as they are more clinically relevant.
- Metformin depletes B12 levels.

SYMPTOMS OF B12 DEFICIENCY

- Weakness
- Fatigue
- Strange sensations, numbness, or tingling in the hands, legs, or feet
- Difficulty walking (staggering, balance problems)
- Anemia

- Swollen, inflamed tongue
- Yellowed skin, jaundice
- Difficulty thinking and reasoning (cognitive difficulties) or memory loss
- Paranoia or hallucinations

FOUR STAGES OF B12 DEFICIENCY

- Stages one and two: Plasma and cell stores of B12 become depleted, and the concentration of holotranscobalamin-2, or holoTC, is reduced.
- Stage three: Elevated homocysteine and urinary or serum MMA concentrations. I've found urine MMA to be a more sensitive marker than serum MMA, but consider the clinical picture. In impaired kidney function, serum MMA would probably be more accurate, but if the patient has SIBO or gut dysbiosis, urine MMA would be more accurate.
- Stage four: The clinical signs and symptoms of B12 deficiency become evident, such as macrocytic anemia and symptoms such as peripheral neuropathy or brain fog.

METHYLMALONIC ACID

Serum and urine MMA can be run. The Organix comprehensive profile from Genova has urine MMA, and serum MMA is available through LabCorp, Quest, and other conventional labs.

- I use the provided lab range for serum MMA. Remember it's an inverse marker. MMA is high in vitamin B12 deficiency.
 - Serum < 300 mol/L, urine < 1.5 mcg/mg
- Genova Diagnostics' lab lists a normal reference range for urinary MMA of less than 2.3 mcg/mL of creatinine with a suggested optimal range below 1.7, yet a study with elderly subjects suggests that a value of 1.5 may be a better threshold for detecting clinical B12 deficiencies.

SERUM HOMOCYSTEINE

- I have set the lower end of the functional range to be 7 (μmol/L).
- High homocysteine levels are not specific to B12 deficiency. It may indicate deficiency of folate, B12, or both.

SERUM B12

- Lower end of B12 functional range is 450 pg/mL.
- Be aware that a high serum B12 does not necessarily rule out functional or active B12 deficiency. Some clinicians view high serum B12 in the absence of any supplementation as a sign of impaired B12 metabolism and possibly low active B12 levels, and I have seen this several times in my practice.

- It's really important to be aware that evaluating patients' B12 status using only MMA, homocysteine, and serum B12 may still miss cases of B12 deficiency.

Once B12 deficiency gets to the final stage, it can cause megaloblastic or macrocytic anemia. At that point, you'll see other markers of B12 deficiency in the comprehensive blood chemistry or CBC, such as low red blood cell count, low hemoglobin, low hematocrit, and elevated MCV, MCHC, MCH, and RDW, and we'll cover these in more detail in the macrocytic anemia unit.

PERNICIOUS ANEMIA

- Consider running intrinsic factor antibodies on patients with low B12.
- Intrinsic factor antibodies approach 100 percent specificity, so if it's positive, you can be virtually sure they have it. However, they are only 50 to 70 percent sensitive, so that test would miss 30 to 50 percent of patients with pernicious anemia.
- Elevated serum gastrin levels, low pepsinogen I levels, and a low ratio of pepsinogen I to pepsinogen II are highly sensitive for diagnosing pernicious anemia, but those tests lack specificity. If one of those is positive and intrinsic factor antibodies are negative, you can't really confirm the diagnosis of pernicious anemia without further workup.
- Pepsinogen is also not widely available in the U.S.
- I usually follow up with serum gastrin and intrinsic factor antibodies.

Testing for pernicious anemia is clinically relevant because patients who have pernicious anemia need to supplement for the rest of their lives, even after addressing other conditions that may impair B12 absorption. It helps patients take B12 deficiency seriously and stay consistent with supplementation. Patients with pernicious anemia will need sublingual B12 supplements or B12 injections because they don't absorb B12 orally through food or oral supplements.

The treatment of B12 deficiency falls into two main categories:

1. **Inadequate intake**, primarily vegetarians and vegans
2. **Impaired absorption**, which can be GI issues such as hypochlorhydria, celiac disease, IBD, or dysbiosis; pernicious anemia; alcoholism; or pancreatic insufficiency.

There is no known tolerable upper intake level for B12, and no toxicity threshold has been found. Therefore, I believe it's safer to advise higher intakes than lower intakes.

HIGHEST DIETARY SOURCES OF B12

Food	Amount (mcg per 100g)
Clam	99
Lamb liver	90
Beef liver	83
Duck liver	54
Oyster	35
Pork liver	26
Caviar	20
Mackerel	19
Herring	19
Mussel	12
Crab	11
Sardine	9
Salmon	6

DO THE FOLLOWING TO INCREASE B12 ABSORPTION

- Address GI issues
- Supplement with Betaine HCl
- Drink cranberry juice
- Increase calcium from food sources

AVOID THE FOLLOWING WHICH DECREASE B12 ABSORPTION

- Alcohol
- Metformin
- Acid-suppressing drugs

THERE ARE FOUR TYPES OF SUPPLEMENTAL B12 AVAILABLE

1. Methylcobalamin, which is a natural form.
2. Hydroxocobalamin, which is a natural form.
3. Adenosylcobalamin, which is a natural form.
4. Cyanocobalamin, which is a synthetic form that can be converted into adenosylcobalamin and methylcobalamin, but its **bioavailability is poor** compared to the other forms.

I think the best approach is probably to use all three natural forms together.

- Ensure adequate folate when supplementing with B12.
- Methylcobalamin is formed and regenerated with the methyl group provided by 5-methylfolate or SAM-e.
- Lithium is another nutrient that must be present for adequate B12 metabolism.
- Can supplement with 5 mg of lithium orotate per day, which is a much lower dose of lithium than the one that is used in mental health disorders.

I like Designs for Health Trifolamin, as it has all three natural forms of B12 with a combined dose of 3 mg plus 400 mcg of Quatrefolic, a form of active folate. It is a sublingual form, so it can be used by patients with pernicious anemia and other absorption issues.

Appropriate therapeutic doses are 3 to 5 mg per day, with little to no concern of overdose.

- Consider adding Betaine HCl supplement to increase B12 absorption. Remember that HCl is contraindicated with gastric or duodenal ulcers and patients who are taking NSAIDs.
- Retest after 60 days. Treatment ranges from 2 months to ongoing.
- Consider B12 injections for patients not responding to oral or sublingual therapy.
- Hydroxocobalamin at a dose of 1 mg (1,000 mcg) per day.